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ONTOGENY OF PERCEPTION OF MATERNAL AND NOSOCOMIAL STIMULI IN INFANTS

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Ontogeny of perception of maternal and nosocomial stimuli in infants
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To Amelie and our wonderful children Fabian and Hedda

ABSTRACT

Preterm born infants in neonatal units experience unusual sensory inputs that can shape and nurture their developing brains differently from full-term healthy newborn infants. To improve the care of preterm infants and their neurodevelopmental outcomes, we need to understand how the brain functions at different developmental stages and implement this knowledge into clinical care and follow-up programs. An infant's cortical response to external stimuli can be measured with functional near-infrared spectroscopy (fNIRS). We aimed to analyze how maternal and nosocomial stimuli are processed in the developing cerebral cortex in infants.

In paper I, the functional cortical processing of a known face (the infant's mother) and an unknown face were assessed at six to ten months of age with fNIRS. We found that the infants exhibited an increased brain response when they saw their mother's face, as compared to the unknown face.

In paper II, we aimed to study the regional cortical responses to known and unknown faces, to compare them between infants born extremely preterm and infants born full-term and to correlate them to regional brain volumes. The infants were examined at six to ten months of corrected age using fNIRS. We also performed structural brain magnetic resonance imaging in the preterm group and correlated their regional cortical volumes to their fNIRS responses. The preterm infants had a smaller hemodynamic response in the right frontotemporal area while viewing a face they knew than the full-term born infants. There was a negative correlation between the hemodynamic response in the right frontotemporal cortex and regional grey matter volume in the face processing areas.

In paper III, we examined the effects of alien odors on preterm and full-term newborn infants, exploring whether these odors elicit pain, and if oral glucose modulates this pain. We exposed the infants to odorous stimuli from the hospital environment and recorded pain behaviors and cortical activation with fNIRS. We repeated the exposure and measurements after oral glucose administration. Newborn infants exhibited brain responses to both olfactory and nociceptive processing areas from 31 weeks of postmenstrual age and also demonstrated pain behaviors. Oral glucose inhibited pain behaviors and cortical activation.

In paper IV, we studied the cortical processing of maternal breast odors in preterm and full-term newborn infants. Three groups of infants, very preterm, late preterm and full-term, were exposed to their mother's breast odor and a control odor during fNIRS measurements. Full-term infants demonstrated bilateral activation of their olfactory cortices following exposure to the maternal breast odor. Late preterm infants and very preterm boys exhibited unilateral cortical activation, unlike very preterm girls.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following original articles and manuscript, which will be referred to by their Roman numerals.

I. **Carlsson J**, Lagercrantz H, Olson L, Printz G, Bartocci M.
Activation of the right fronto-temporal cortex during maternal facial recognition in young infants. *Acta Paediatr,* 2008;97:1221-5.

II. **Frie J**, Padilla N, Ådén U, Lagercrantz H, Bartocci M.
Extremely Preterm-Born Infants Demonstrate Different Facial Recognition Processes at 6-10 Months of Corrected Age. *J Pediatr,* 2016. 172: p. 96-102 e1.

III. **Frie J**, Bartocci M, Lagercrantz H, Kuhn P.
Cortical Responses to Alien Odors in Newborns: an fNIRS Study. *Cerebral Cortex*, 2017:1-12 https://doi.org/10.1093/cercor/bhx194

IV. **Frie J**, Bartocci M, Lagercrantz H, Kuhn P.
Ontogeny of cortical perception of maternal breast odors in newborn infants: A fNIRS study
-*Manuscript*

CONTENTS

LIST OF ABBREVIATIONS

ASD	Autism spectrum disorder
BPD	Bronchopulmonary dysplasia
CVI	Cerebral visual impairment
EEG	Electroencephalogram
ERP	Event-related potentials
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near-infrared spectroscopy
HbO_2	Oxygenated hemoglobin
HHb	Deoxygenated hemoglobin
IOD	Inter optode distance
IVH	Intraventricular hemorrhage
MBO	Maternal breast odor
MEG	Magnetoencephalography
MRI	Magnetic resonance imaging
NFCS	Neonatal facial coding system
NICU	Neonatal intensive care unit
NIDCAP	Newborn individualized developmental care and assessment program
NIR	Near-infrared
NIRS	Near-infrared spectroscopy
OFC	Orbitofrontal cortex
PDA	Patent ductus arteriosus
PVL	Periventricular leukomalacia
SC	Somatosensory cortex

1 INTRODUCTION

All births that occur before week 37+0 of gestation are defined as preterm births. In Sweden, the incidence of preterm births has been stable at around 5% for the last few decades and active treatment to rescue preterm born infants can be initiated for babies from the 22nd week of gestation (Lundqvist et al. 2014, Domelof et al. 2016). Extremely preterm born infants (born < 28 weeks) and very preterm infants (born between 28-32 weeks) are at "high risk for brain hemorrhages, white-matter injuries, poor brain growth, and for subsequent neurodevelopmental impairment" (Vohr and Allen 2005). The Swedish EXPRESS follow-up study focused on extremely preterm infants born between 2004-2007 and found that at 2.5 years of age, 27% had moderate or severe disabilities, compared to 3% in the control group born at full term, and that their neurodevelopmental outcomes improved within every week of gestation (Serenius et al. 2013).

One of the primary goals for neonatal care is to promote brain wellbeing and to limit all possible risks for the developing brain. The sensory environment around the infant plays a crucial role in brain development and the infant's future sensory adaptation (Knudsen 2004). Sensory experiences can impact the newborn infant's health status and brain development. The sensory environment, therefore, needs to be controlled by the neonatal intensive care unit (NICU) staff, both to improve the current state of the newborn infants and to support their long-term neurodevelopmental outcome. These days both acute and chronic pain and discomfort are routinely evaluated in many NICUs by using different pain scales that measure behavioral and physiological parameters. However, a large European study found that daily pain assessments were only performed in 10% of neonates (Anand et al. 2017). Awareness of pain in the early phases of the neonatal period, and the association between pain and the processing of other sensory cues such as olfactory and trigeminal stimuli, are still not fully understood. Olfactory or visual inputs are not as easy to evaluate and are usually not controlled for in clinical routines, but these sensory inputs can also have both short-term and long-term effects on the infant. Preterm infants in NICUs are exposed to nosocomial odors that could cause them harm and odors originating from their parents that could support their wellbeing.

Extremely preterm infants often suffer from different neurodevelopmental problems when they grow up, including autism spectrum disorder (ASD) (Johnson et al. 2010, Lampi et al. 2012). One problem for children with ASD can be an inability to recognize faces, an issue that can also be found as an isolated event among children born extremely preterm (Dutton and Jacobson 2001). The processing of visual inputs in the developing cortex can be disturbed for preterm infants treated in the NICU and this could impact their future visual processing abilities.

This thesis presents a series of studies that investigated the neurodevelopmental effects that different maternal and nosocomial visual and olfactory stimuli had on infants born at different

gestational ages. Functional measures of brain activation were measured using functional near-infrared spectroscopy (fNIRS).

2 BACKGROUND

2.1 PERINATAL BRAIN DEVELOPMENT

The cerebral cortex plays a vital role in the perception of sensory input, cognition, memory and consciousness (Lagercrantz 2010, Purves 2012). The preterm infant can be aware of their sensory inputs from around the 24th week of gestation, which is when the thalamocortical connections have been established (Kostovic and Judas 2010, Lagercrantz 2016). This is a crucial landmark, as the infants can by then be considered to fulfill the basic criteria for being conscious: being awake, aware of themselves and the environment (Lagercrantz 2014). The neurons in the cerebral cortex are born in the ventricular zone and then migrate to form the cortex from the cortical subplate (Rakic 1988). The cortex is developed during the last trimester and shaped into six layers, starting with the inner layer through which migrating cells pass to form the outer layers (Geschwind and Rakic 2013). Gyrification of the cortex starts at around the 26th week of gestation due to cortical growth. Brain development at this early stage can be disturbed by genetic and environmental factors and infants born preterm will experience an entirely different environment than fetuses remaining in the womb. In Figure 2.1 the major neurodevelopmental processes are schematically presented.

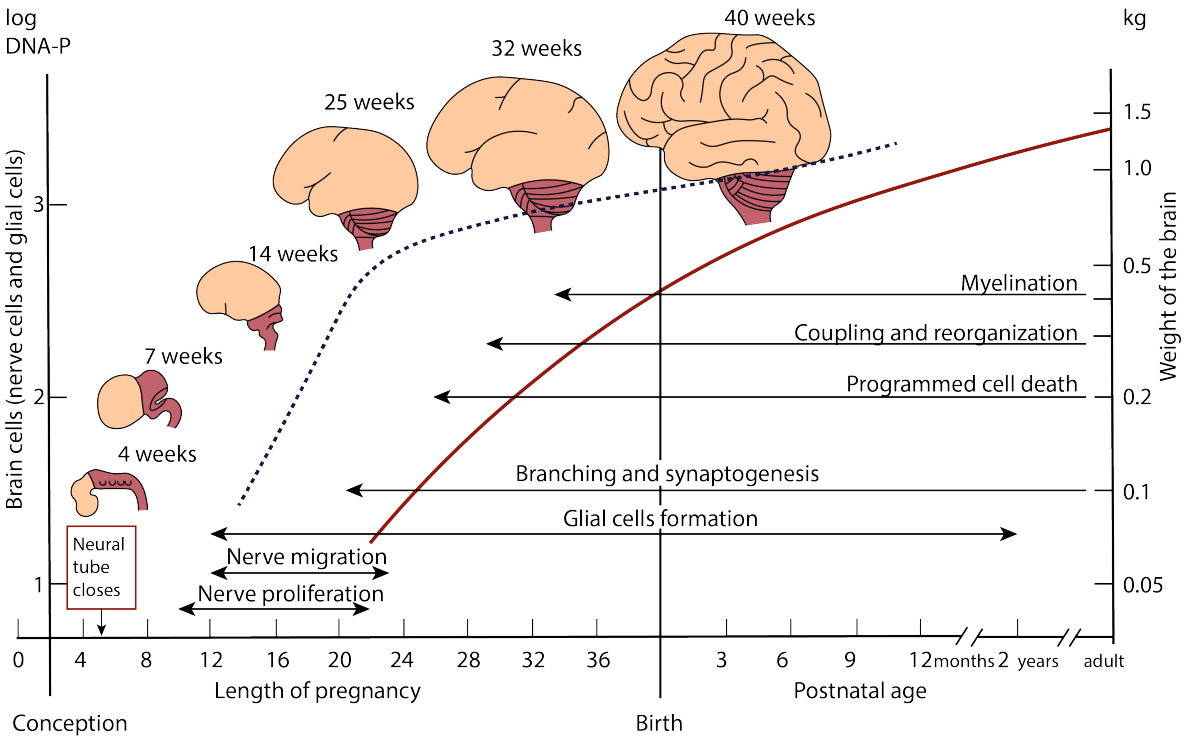

Figure 2.1. *Milestones of brain development, reproduced and modified with permission from (Lagercrantz 2016)*

In early development, the organization of the cortical neurons is not very precise, with connections between several parts of the brain that serve no purpose. The organization is action dependent and also dependent on programmed cell death (apoptosis). Neurons receiving input from the sensory organs will fire and then survive and organize in functional pathways.

Extremely preterm infants spend a long time being cared for in NICUs, where they are unnaturally separated from their parents and all the biologically meaningful sensory cues related to them, including olfactory signals and visual stimulation. Moreover, the sick newborn infant in a NICU experiences a multitude of atypical stimuli, such as painful and tactile stimulations, nosocomial olfactory and gustatory stimulations, extensive exposure to strong light sources, exposure to a large number of faces and more. Compared to full-term infants, extremely preterm infants have reduced brain growth with reductions in the global cortical volumes, but also increased volumes in visual processing areas (Padilla et al. 2014). In this study, clinical risk factors, such as increasing prematurity and mild intraventricular hemorrhages (IVH), affected the reductions in brain growth even more and the authors speculated that the longer extra-uterine experience with visual stimuli might explain the increased growth of the visual processing areas.

The care provided in NICUs has developed considerably during the last few decades, especially the care related to the infant's sensory environment. In the 1980s a method called the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) (Als et al. 1986) was presented and since then it has been implemented around the world. NIDCAP has been shown to have effects on the length of hospitalization (McAnulty et al. 2009, Ohlsson and Jacobs 2013), improvements on Bayley mental and psychomotor developmental scores (Westrup et al. 2000, Als et al. 2004, McAnulty et al. 2009) and improved neurological markers seen on magnetic resonance imaging (MRI) and electroencephalograms (EEGs) (Als et al. 2012). The goals of the program are to reduce stressful events, promote neurobehavioural organization and increase the parents' understanding of their infants and support them as primary caregivers. It involves adapting the care of the infants autonomic and conscious state, by, for example, covering the incubator with a dark blanket, supporting the infant in the fetal position with a nest, coordinating painful procedures to a few time points, protecting the infants from noise and involving the parents in their care. Several other programs have also been developed with similar content.

2.2 BRAIN ACTIVATION - FUNCTIONAL STUDIES

How sensory inputs are processed in the developing brain is not fully understood. Several studies have investigated how both fetuses and preterm infants behave following sensory stimulation. However, as behaviors do not need to be governed by the cortex, a withdrawal movement can either be a spinal reflex, which is not processed in the brain or processed subcortically, or it can be a conscious movement involving higher brain areas and a very high level of consciousness. Other studies have used purely anatomical measures resulting from autopsies or brain imaging techniques. The most accurate way to measure brain activation is by using invasive techniques that measure neuronal activity. By inserting electrodes into the brain, it is possible to measure spiking activity in a single neuron or in units. However, invasive techniques put subjects at risk and are rarely used in research with human subjects. Neuronal electric activity can also be measured with noninvasive techniques, such as an EEG or magnetoencephalography (MEG). Event-related potentials (ERP) can be used to study functional brain activity related to sensory inputs, as this method reflects the total electrical effects in large populations of neurons. These methods have high temporal resolution and can measure rapid changes, but the spatial resolution is lower. Non-invasive techniques must be used to enable us to understand the development of the cerebral cortex and conscious processing in infants. During the last few decades, several functional methods have been developed and used in infant studies. Functional methods measure brain responses to a stimulus, either sensory, motor or cognitive, and by using such methods we can investigate how the brain reacts at different gestational ages and at different stages of development. In our studies, we aimed to measure functional brain responses to nosocomial and maternal stimuli in the cerebral cortex where consciousness is thought to take place (Lagercrantz and Changeux 2009, Koch et al. 2016).

2.2.1 Coupling

The relationship between neuronal activity, metabolism and blood flow can be used to study functional neuronal activity. Blood vessels are linked to neurons to guarantee an appropriate energy flow to the cells during shifts in neuronal activity. The relationship between neuronal activity and the supportive substrates of glucose and lactate is called neurometabolic coupling. During neuronal activity, glucose levels decrease and lactate levels increase in the tissue that can be measured (Li and Freeman 2015). In positron emission tomography, this fact can be used to localize areas with higher or lower metabolic demands, by connecting radioactive molecules to glucose molecules. This technique generally provides a higher spatial resolution than EEG, but it also provides a lower temporal resolution and is not well tolerated by infants.

Neuronal activity can also be measured using the hemodynamic response. The relationship between electric activity, the metabolic response and the hemodynamic response is called neurovascular coupling. When glucose levels in the cells decrease during spiking the increased glucose demand is served by regulated blood flow (Iadecola 2017). Typically,

neuronal activity leads to an increase in oxyhemoglobin (HbO_2) and a decrease in deoxyhemoglobin (HHb). See Figure 2.2 for a graphical explanation.

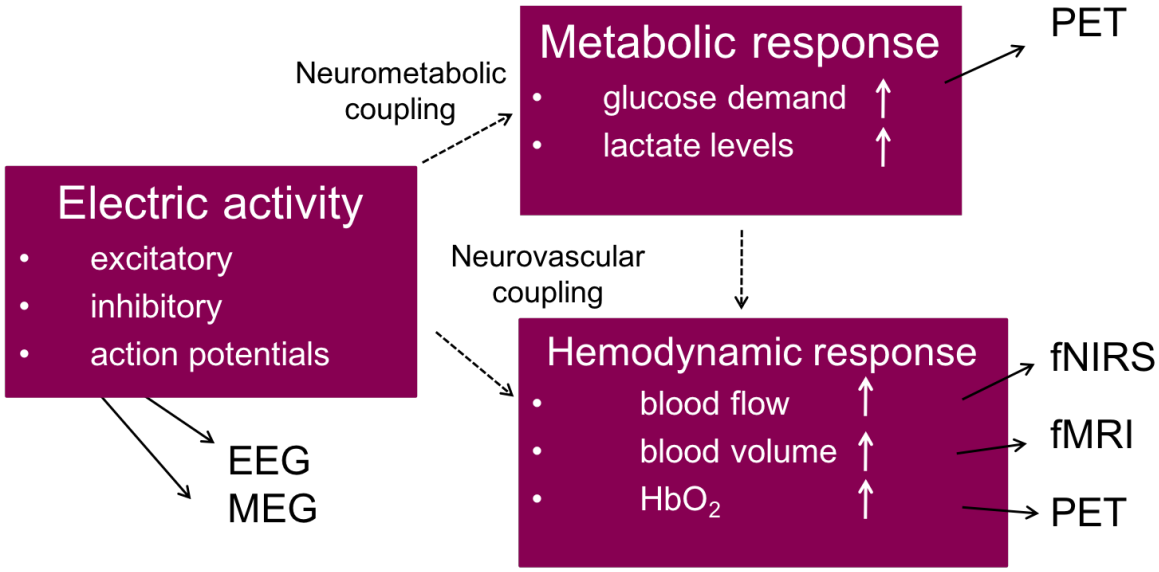

Figure 2.2. *Flowchart of possible measures of neuronal activity and possible techniques.*

The gold standard method that is now used to perform functional measures of brain activity is fMRI. This neuroimaging technique measures a component, blood oxygen level, which is dependent on the hemodynamic response, which is in turn related to neuronal activity (Ogawa et al. 1990). However, it is not easy to use in infants and only a few studies have been performed. Even though it is noninvasive, it is a complicated procedure to put a fragile infant into a magnetic resonance imaging camera and the infants need to be fixated and asleep or sedated in order to be investigated.

2.3 NEAR-INFRARED SPECTROSCOPY

Near-infrared spectroscopy (NIRS) is another method that also uses the hemodynamic response to neuronal activity as a substrate to measure cortical activation. This technique was initially developed by Jöbsis (Jobsis 1977) in the late 1970s and has evolved into a highly sophisticated neuroimaging technique during the last decade. The skull and brain are relatively transparent to near-infrared (NIR) light of different wavelengths (650-1000nm), which is absorbed by different chromophores (light-absorbing molecules) in the bloodstream. Hemoglobin is the dominant chromophore and the way it absorbs NIR light varies with oxygenation (Figure 2.3.1).

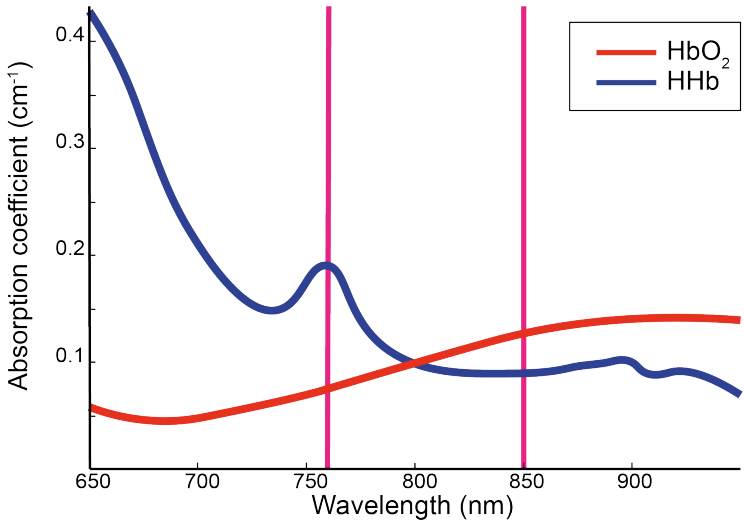

Figure 2.3.1. *The absorption spectra of HbO_2 and HHb in the near infrared wavelength range. The purple vertical lines are the wavelengths used by the NIRx device described in papers III & IV.*

The simplest form of NIRS measurement consists of a device with one emitting optode and one receiving optode (comprising one channel) located 2-5 cm from each other and measuring cerebral oxygenation in a specific area. Most of the photons that leave the emitting optode will be absorbed by the superficial layers above the cortex, including the scalp, skull and cerebrospinal fluid. The remaining photons will travel along a banana-shaped trajectory in the cortex, where they will be absorbed by hemoglobin molecules or scattered away (Figure 2.3.2). The scattering remains constant and the only loss of light will be because of absorption (attenuated energy) by the main chromophores. Attenuation of HbO_2 and HHb in the tissue can be calculated using the Beer-Lambert law (Villringer and Chance 1997). This kind of measurement can be used to evaluate the functional response to a specific stimulus and that is why it is called functional NIRS (fNIRS). The typical hemodynamic response to neuronal stimulation shows an increase in HbO_2 and a decrease in HHb (Figure 2.3.3) (Villringer and Chance 1997).

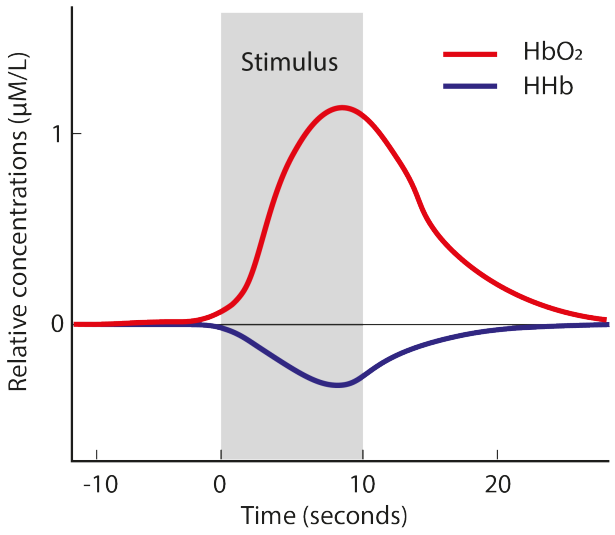

Figure 2.3.3 *Typical pattern in the fNIRS response due to neuronal activity.*

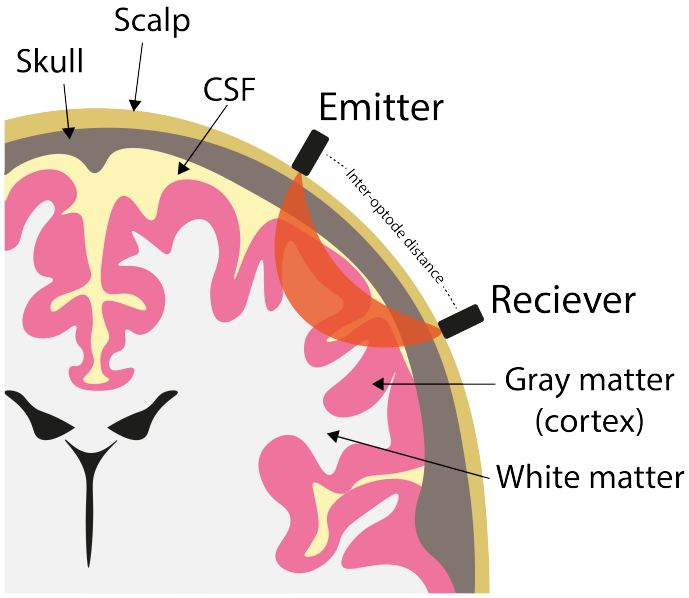

Figure 2.3.2. *Near-infrared light travels in a banana shape from the emitting optode to the receiving optode through cerebral tissue. The depth of the light is dependent on the inter-optode distance.*

2.3.1 Resolution and positioning

Basic fNIRS measurements have quite low spatial resolution compared to other techniques. However, most of the fNIRS systems that are currently available use multiple emitting and receiving optodes to allow the extended cortical areas to be examined at a higher spatial resolution. In general, the inter optode distance (IOD) decides the depth and size of a channel and an increased IOD allows measurements of deeper brain tissues, but at the expense of the signal-to-noise ratio (Calderon-Arnulphi et al. 2009). In infant studies, the typical IOD used has been 20-40 mm (Lloyd-Fox et al. 2010), but the optimum separation is a matter of debate. Several factors could influence the choice of IOD, such as the number of optodes used, the intensity of the light source, the age of the infants, the thickness of the superficial layers and the area of the cortex being examined. The optodes can be arranged in such a way that one receiving optode can receive inputs from several emitting optodes, allowing more channels than optodes and measurements with different IODs and depths (Blasi et al. 2007). Results from multiple channel fNIRS measurements can be presented as 2D or 3D maps with a high spatial resolution of 10mm (Mahmoudzadeh et al. 2013, Ferradal et al. 2016). fNIRS has a relatively high temporal resolution compared to fMRI, which typically ranges from 2-10 (up to 100) Hz.

One weakness with fNIRS measurements is that there is no possibility of measuring brain structures for anatomical references. To assure that the fNIRS measurements are from the cortical areas of interest, it is important to locate the optodes carefully on the skull. External landmarks of the skull can be translated to cortical structures using the 10-20 EEG system and MRI maps (Kabdebon et al. 2014).

2.3.2 Processing of fNIRS data

The first step in the data processing is to assure high enough quality in each channel. Then a major step is to sort out artifacts and possibly correct them. Artifacts can arise from movements and systemic physiological influence. Movement artifacts can be limited using a secure cap design, but will be present when investigating infants who are awake. These artifacts are typically abrupt changes in the signal that occur simultaneously in several channels. The most direct method for artifact correction is to reject all trials affected by artifacts. However, as infants are hard to control in a study setting, and they often move, this method often results in exlcuding a large number of data sets. Different hardware has been used to improve the data, using accelerometers (Virtanen et al. 2011) or short-separation channels (Brigadoi and Cooper 2015). There are also several filtering or software-based techniques that can correct for artifacts (Hu et al. 2015). Low-pass filtering can remove high-frequency noise, such as the cardiac signal and high-pass filtering signal drift. Artifacts can also be accounted for manually by visual inspection of the hemodynamic curves and identifying spikes or values over a set threshold value (Lloyd-Fox et al. 2009).

2.3.3 fNIRS and infant studies

fNIRS is well suited for use for an infant population, as NIR light penetrates to deeper brain regions in smaller heads. It is also easy to use at the infant's bedside with minimal harm to them due to noise or the need for sedation, unlike with fMRI. Typically, the optical fibers are fixed onto the infant's head using an elastic cap and the head does not need to be fixated. In comparison to EEG, fNIRS has a much higher spatial resolution and is less sensitive to motion artifacts.

2.3.4 Clinical use

Preterm infants' brains are examined in several ways in the NICU. Ultrasound, computed tomography and MRI are commonly used imaging techniques to find hemorrhages or lesions in the brain. Brain function is commonly assessed using EEG or amplitude-integrated EEG (Hellstrom-Westas and Rosen 2006). NIRS can be used as a clinical tool to monitor cerebral oxygenation. When measures of cerebral oxygenation are combined with treatment guidelines, cerebral hypoxia and brain injuries can be avoided (Hyttel-Sorensen et al. 2015). Simultaneous NIRS and EEG recordings can also be a valuable tool with regard to managing seizures (Wallois et al. 2010). fNIRS can also be used as a clinical tool in the NICU, to identify cerebral hemodynamic changes in patients with vascular disorders, such as IVH, and it may identify abnormalities before they are visible on an EEG (Mahmoudzadeh et al. 2018).

fNIRS could also be used to detect atypical brain responses to social stimuli in children at risk for ASD or attention deficit hyperactivity disorder (Lloyd-Fox et al. 2013, Ichikawa et al. 2014).

2.4 FACIAL RECOGNITION

Social interaction is essential for all human beings and a key element of this is the ability to recognize faces. When we see a familiar face, it takes less than a second for us to recognize who that person is and whether we want to speak to them or avoid them. The ability to recognize faces is already present at birth to some extent, as newborn infants turn their heads and eyes towards face-like structures (Johnson et al. 1991, Valenza et al. 1996) and can imitate facial gestures (Meltzoff and Moore 1977). Infant-parental bonding is facilitated by face-to-face interaction and the ability of infants to turn their head and gaze towards faces is essential.

Facial recognition depends on the ability to process visual inputs from the photoreceptors that converge to the ganglion cells in the retina. These cells have been shown to demonstrate spontaneous activity as early as fetal life (Shatz and Stryker 1988). Basic visual processing takes place in the occipital lobe. Visual recognition is a more complicated task, mediated by the ventral stream that runs from the occipital lobe to the temporal lobe where faces are processed in specific areas. fMRI studies in adults have identified that the middle fusiform gyrus, superior temporal sulcus, anterior temporal lobe and the inferior occipital gyrus are core areas for facial recognition (Kanwisher et al. 1997, Haxby et al. 2000, Von Der Heide et al. 2013). These areas have been reported to be activated following facial stimuli in infants (Farroni et al. 2002, Tzourio-Mazoyer et al. 2002, Otsuka et al. 2007, Nakato et al. 2011, Guy et al. 2016). However, most studies about infants' interests in faces have been behavioral and measured head turns or fixation time and have not referred the neural basis for these findings. In 1991, Morton and Johnson developed a theory (Morton and Johnson 1991) that suggested that the preference for faces was served by a sub-cortical route, which controlled the visual inputs to the developing cortical circuits and supported the development of specialization for faces during childhood and adolescence. However, there is a debate about whether this preference for faces at birth is triggered by the actual face or by biases toward structural properties of visual stimuli (Johnson et al. 2015, Simion and Giorgio 2015). Several studies have investigated different biases, including Turati et al., who found that newborn infants were more likely to be engaged by nonfacelike stimuli with more elements in the upper part than facelike stimuli with more elements in the the lower part (Turati et al. 2002). This kind of stimuli has even been shown to engage fetuses in the third trimester, suggesting that postnatal experience is not required for this bias (Reid et al. 2017). Newborn infants also prefer to look at stimuli with congruent relationships between the shape and the orientation of the boundaries and the disposition of the inner properties (Cassia et al. 2008). However, one study showed that, at three months of age, infants preferred actual faces over scrambled face configurations with more elements in the upper part, suggesting that their visual experiences during these first months changed their perception of faces (Turati et al. 2005). By this age, the first cortical processes of face stimuli have also been recorded (Tzourio-Mazoyer et al. 2002, Halit et al. 2004). The development of the cortical face areas then continues during the first months and even years of life (Pascalis et al. 2011).

Facial recognition is a sophisticated visual processing ability and dysfunction of this ability can be entirely separate from other visual disabilities. The inability to recognize faces, which is known as prosopagnosia, is a fairly unknown problem among the general public. However, it can be a large social handicap for those affected, because of difficulties in recognizing friends and family and participating in social activities. This can lead to anxiety, feelings of embarrassment and a very limited social circle. Those affected have to use other methods and tools to identify a person, such as their hairstyle, glasses, clothes, odors or voice. Prosopagnosia can be part of a neurodevelopmental disorder, such as ASD or cerebral visual impairment (CVI), or an isolated problem. It can be both congenital/developmental or acquired and up to 2.5% of the population can be affected (Behrmann and Avidan 2005, Kennerknecht et al. 2006, Dalrymple et al. 2012, Corrow et al. 2016). The acquired form of prosopagnosia can have many different etiologies, such as strokes, tumors, infections, temporal lobe resections or traumas (Corrow et al. 2016). Patients with developmental prosopagnosia have impaired functional connectivity between the different cortical areas involved in face processing and not just impaired function in the actual areas (Zhao et al. 2017). Early diagnosis can be important, to help the individual overcome psychological problems and find other ways to identify people they know.

Preterm infants can suffer from brain injuries that involve the areas that are important for facial recognition, but their altered sensory input during their stay in the NICU can also affect the development of these areas. Preterm infants are at risk of developing prosopagnosia and infants with periventricular leukomalacia or bronchopulmonary dysplasia have an even higher risk (Dutton and Jacobson 2001, Fazzi et al. 2009, Potharst et al. 2013). Preterm infants with low birth weights, namely those below the 10^{th} centile, have been found to score worse on face recognition tests than those with an appropriate birth weight (Perez-Roche et al. 2017).

2.5 ODOR PERCEPTION

2.5.1 Olfactory system and cortical processing of odors

Odor perception starts in the nose, which develops between the fourth and the eighth week of gestation (Muller and O'Rahilly 2004). In the nasal cavity, cilia project out of the olfactory epithelium into a mucus layer. Olfactory receptors in the mucus membrane, located on the olfactory sensory neurons, are the first elements in odor perception (Buck and Axel 1991). Each olfactory receptor recognizes multiple odors and each odor is detected by different combinations of olfactory receptors (Malnic et al. 1999). More than 600 olfactory receptor genes have been identified and these are unevenly distributed on 21 human chromosomes, representing more than 3% of the human genome (Malnic et al. 2004, Axel 2005). Olfactory recognition is thereby highly prioritized in our species, with a large number of genes maintained. Olfactory sensory neurons form axons that are bundled into groups and penetrate the ethmoidal cribriform plate to reach the olfactory bulb, where they form synaptic glomeruli. Olfactory receptors of the same type are randomly distributed in the mucosa, but converge on the same glomeruli. The glomeruli are connected in groups to mitral cells whose axons project into the olfactory cortex along the olfactory tract (Figure 2.5.1).

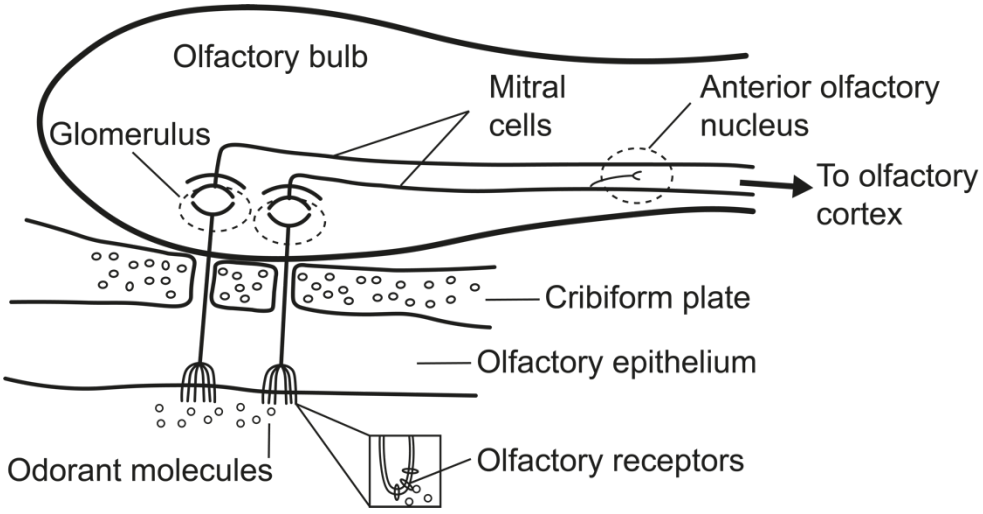

Figure 2.5.1. *Olfactory receptors, the olfactory bulb and the olfactory tract.*

The olfactory bulb starts to develop around the sixth week of gestation, and mitral cells are identifiable around week eight. The olfactory tract is present around week 11 (Muller and O'Rahilly 2004). The bulb is visible on fetal MRI from 30 weeks of gestation (Azoulay et al. 2006). The first contact for the nasal olfactory receptors with fluid-based chemical stimuli starts when the nasal epithelial plug dissolves between 16-24 gestational weeks (Sarnat and Yu 2016). The fetus is then exposed to the odors present in the amniotic fluid. This process is induced by fetal swallowing and breathing from week 22 (Badalian et al. 1993).

Mitral cells in the olfactory tract connect the olfactory bulb to the cerebral cortex directly or through the anterior olfactory nucleus, mostly without a thalamic relay between the receptors and cortex. The olfactory bulb incorporates its equivalent to the thalamus, both with the interneurons in the bulb and the anterior olfactory nucleus. It also connects to the ipsilateral

hemisphere, unlike other sensory inputs processed in the contralateral hemisphere. The olfactory tract terminates in the primary olfactory cortex located on the medial parts of the temporal lobe and the base of the frontal lobe. It also has direct connections to the amygdala, where emotions evoked from olfactory stimuli are mediated. The piriform cortex, located at the junction between the temporal and frontal cortices, is the most significant recipient of input from the olfactory bulb and a major part of the primary olfactory cortex. In Figure 2.5.2 the location of the main areas of the olfactory network can be seen. The piriform cortex is activated following olfactory stimulation in both adults and newborn infants (Zatorre et al. 1992, Adam-Darque et al. 2017). Other areas included in the primary olfactory cortex are the entorhinal cortex, the olfactory tubercle and the amygdala. Input from these structures is sent to the secondary olfactory cortex, directly or through the thalamus. The secondary olfactory cortex comprises the orbitofrontal cortex (OFC), frontal cortex, the insula, the hippocampus, the thalamus, the hypothalamus, the striatum and the pallidum (Lundstrom et al. 2011, Mai and Paxinos 2012). The OFC is the primary recipient of input from the piriform cortex. Discrimination of odors is thought to take place in the OFC.

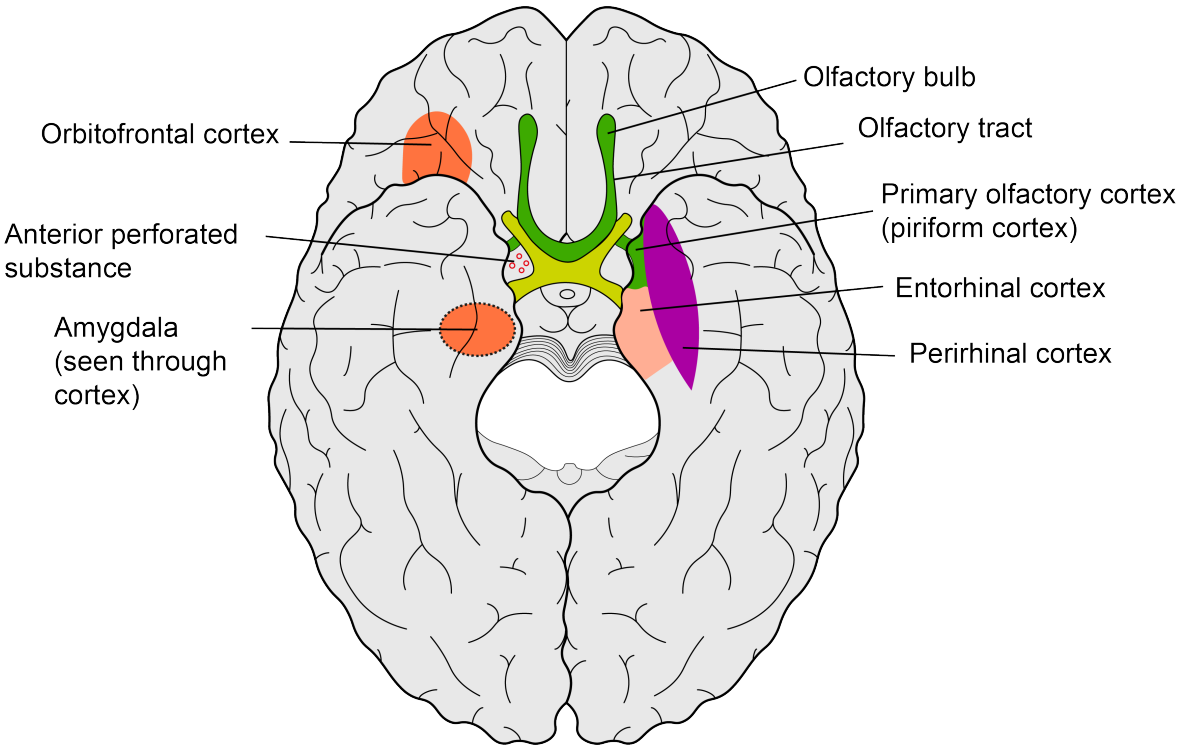

Figure 2.5.2. *Inferior view of the olfactory network.*

Cortical processing of odors in utero has not been described in humans. Preterm infants can be studied to assess the ontogeny of olfactory cortical processing and awareness of odors. In 1978 Sarnat showed that both term and preterm infants responded with a sucking response or arousal to the olfactory stimulus of peppermint (Sarnat 1978). Perception of odors in preterm infants will be discussed further in the following paragraphs.

2.5.2 Odor perception, nosocomial odors

It is not just the olfactory nerve that is involved in odor perception, as the trigeminal nerve has branches in the nose and is sensitive to chemo-stimulants. The trigeminal nerve divides into three branches: the maxillary, the ophthalmic and the mandibular nerve. The olfactory mucosa is innervated by free nerve endings of the ophthalmic and maxillary branches (Anton and Peppel 1991). These branches transfer information to the trigeminal ganglion and then into the brainstem and thalamus. Cortical processing of trigeminal inputs continues in two different networks: the somatosensory cortices (SC) and the prefrontal cortex, insula and the limbic system, including the OFC (Treede et al. 1999, Lundstrom et al. 2011). In Figure 2.5.3 the trigeminal system is visualized. Intranasal trigeminal stimulation then activates both the somatosensory pain areas and the olfactory areas (Boyle et al. 2007, Hummel et al. 2009), and cause a painful sensation (Hummel et al. 2003).

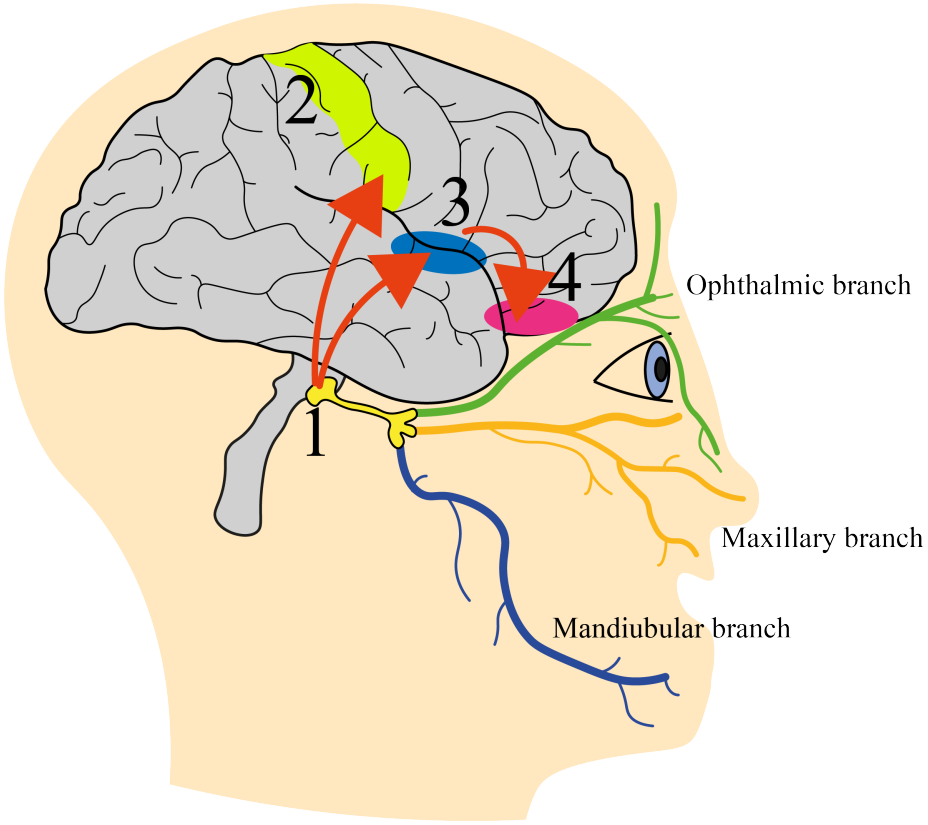

Figure 2.5.3. *Central processing of intranasal trigeminal stimuli. Free nerve endings from the ophthalmic and maxillary branches in the nasal cavity are connected in the trigeminal glomeruli, from where the information is transferred to the trigeminal nucleus (1). From here two separate networks receive information: (i) the somatosensory cortices (2) and (ii) the insula (3) and orbitofrontal cortex (4).*

Most odors stimulate both the olfactory and the trigeminal nerve (Doty et al. 1978), but the trigeminal nerve is particularly sensitive to the odorous components of irritation, pungency and coldness. The intranasal trigeminal system is crucial for survival as it plays a significant role in sensing irritants and potentially toxic chemicals. The trigeminal subsystem starts to develop with chemoreceptors in the nasal cavity around the eighth week of gestation and is

functional around 22 weeks of gestation (Golubeva et al. 1959, Bossy 1980, Schaal et al. 2004). Preterm infants from 31 weeks have demonstrated respiratory and cardiac changes in response to trigeminal air-jet stimulation (Ramet et al. 1990). Behavioral measures based on facial responses have been reported in preterm infants exposed to trigeminal/olfactory stimuli and these infants have also demonstrated changes in their respiratory patterns (Schaal et al. 2004). Exposure to trigeminal nosocomial odors can trigger hemodynamic changes in the olfactory cortex in preterm infants (Bartocci et al. 2001). The concentration of the irritating agent seems to be an important factor in trigeminal processing in newborn infants. Stimulation with low concentrations of eucalyptol agents, which are considered to have a trigeminal component, did not activate trigeminal pathways in full-term infants in a fMRI study (Adam-Darque et al. 2017). In the NICU, preterm infants are exposed to several nosocomial odors that are more or less irritating. In a French survey, Kuhn et al. found that preterm infants treated in NICUs were exposed to nosocomial odors at a mean rate of 44 times a day (Kuhn et al. 2011). Of these odor exposures, 19 were from odors that were known to be irritating and nine were from potentially irritating odors. When they were on a ventilator, the incidence increased even more. These irritating nosocomial odors can stimulate both the trigeminal and olfactory subsystems and interfere with the infant's normal development.

2.5.3 Pain perception and modulation in preterm infants

Painful or irritating stimuli are common in the NICU: in the short term they are related to invasive procedures and in the long term they are due to medical disorders and occur after surgery. The gold standard pain relief used for procedural pain in full-term and preterm newborn infants undergoing procedures such as venipuncture, heel lances or intramuscular injections, is oral glucose or sucrose (Stevens et al. 2016). Studies that used different pain scores to measure responses during and after the procedures mentioned above, such as facial expressions, crying and heart rate, have proved that oral glucose reduced pain. However, the evidence is conflicting for other common procedures, such as subcutaneous injections, arterial punctures, nasogastric tube insertions, bladder catheterization or examining infants for retinopathy of prematurity. The mechanism by which glucose interacts with the nociceptive system in the brain is not fully understood. Glucose might reduce pain through a gating mechanism rather than an analgesic one and the hedonic value of glucose seems to be important when it comes to decreasing pain behaviors (Foo and Mason 2009). In one study, oral sucrose did not seem to affect cortical brain activation in pain areas following a heel lance, although it did decrease the pain score (Slater et al. 2010). However, these findings cannot be generalized and more studies are needed (Stevens et al. 2016). Potential analgesia for trigeminal pain in infants is not well studied. However, intranasal trigeminal pain can be modulated in adults by analgesic agents (Oertel et al. 2008).

fNIRS has been used to assess cerebral activity in pain-related cortical areas following painful stimuli in preterm infants (Bartocci et al. 2006, Slater et al. 2006). It has also been used to assess cortical activity following olfactory stimuli in full-term infants (Bartocci et al.

2000) and irritating odors in preterm, newborn infants (Bartocci et al. 2001). Nociceptive brain activity has also been evaluated in infants using evoked related potentials (ERP) and fMRI (Slater et al. 2010, Goksan et al. 2015). Specific nociceptive brain activity and reflex withdrawal have been found to be correlated to each other, and to be graded with stimulus intensity, but clinical pain scores did not correlate with stimulus intensity (Hartley et al. 2015). There is an ongoing debate about how to evaluate pain and analgesic agents among newborn infants and which methods should be used (Pillai Riddell et al. 2016). In the clinic, behavioral/physiological pain scales are the most common method, but composite measures are more common in research, including the measurement of specific brain activity.

2.5.4 Odor perception, maternal odors

Odors from the mother's diet are the first odors that fetuses experience in the womb. When the nasal epithelial plug is dissolved, amniotic fluid can flow through the nose and the fetus starts to "smell" it. Behavioral data has shown that full-term newborn infants preferred anise over a control odor immediately after birth and on day four if their mothers had consumed anise in the last two weeks before her due date (Schaal et al. 2000). A similar effect was also seen at six months of age for infants exposed to carrots through amniotic fluid or breast milk (Mennella et al. 2001).

Maternal body odors (MBOs) are usually the first odors presented to the newborn infant after birth. The areola is densely supplied with different skin glands that produce different kinds of odors, namely apocrine sweat glands, lactiferous glands and sebaceous glands. The vascular anatomy of the areola gives it a higher temperature than the nipple and the rest of the breast, which can increase the evaporation of olfactory molecules. These odors are essential to attract the infant and stimulate early attachment (Doucet et al. 2007). MBOs are vital for nipple localization and the start of feeding. One study found that significantly more newborn infants moved towards a breast with natural MBOs and started feeding than a washed breast (Varendi et al. 1994). This was also seen when the breast odor was presented on a cotton pad (Varendi and Porter 2001). Infants can also differentiate between their own mother's breast odor and another mother's and this recognition is enhanced by early skin-to-skin contact and by that maternal odor exposure (Mizuno et al. 2004).

MBOs, breast-milk odors and skin-to-skin contact are clinically useful, as they have been shown to have a calming effect on infants during venipuncture or heel lance procedures (Nishitani et al. 2009). This effect has also been seen in preterm infants (Badiee et al. 2013, Olsson et al. 2016). Preterm infants exposed to their mother's milk odor breastfed more effectively (Raimbault et al. 2007) and preterm infants with increased skin-to-skin time attained full breastfeeding faster (Oras et al. 2016).

3 AIMS

The overall aim of this thesis was to investigate cortical responses to maternal and nosocomial sensory inputs in newborn infants and children born prematurely using functional near-infrared spectroscopy.

Specific research objectives:

3.1 PAPER I

- To assess the cortical responses of children aged six to 10 months when they were exposured to an image of their mother's face and an unknown face.

3.2 PAPER II

- To compare regional cortical responses to known and unknown faces among children born extremely preterm and full term.
- To correlate these functional cortical responses to regional cortical volumes in extremely preterm born children at term-equivalent age.

3.3 PAPER III

- To investigate if very preterm and full-term infants perceived trigeminal/olfactory stimuli at a cortical level.
- To study if nosocomial trigeminal/olfactory stimuli could lead to pain.
- If nosocomial trigeminal/olfactory stimuli led to pain, we aimed to investigate if nonpharmacological treatments, such as oral glucose, could modulate intranasal nociception mediated by the trigeminal system.
- To examine the effect of brain maturation and postnatal experience on the cortical responses and pain-related behaviors.

3.4 PAPER IV

- To investigate if full-term infants could perceive their mother's breast odor at a cortical level.
- To study if preterm born infants could perceive their mother's breast odor at a cortical level.
- To explore if there were any differences in the cortical responses depending on the duration of the infants' intra-uterine lives.

4 METHODS

The specific methods and procedures used in the individual papers are described in detail in each paper.

All the studies in this thesis were observational studies on human infant subjects with predefined characteristics.

All four studies were evaluated and approved by the local ethical committee at the Karolinska Institutet. Parental consent was provided before any infants were included in the studies.

4.1 FACIAL RECOGNITION PAPERS I AND II

4.1.1 Inclusion and exclusion criteria

The full-term born infants included in both studies were born after an uncomplicated delivery and postnatal period. They had a normal neurological status at the routine examinations after delivery and at the healthcare check-ups. They were recruited from child health centers in the Stockholm area and the orthopedic follow-up clinic at Astrid Lindgren Children's Hospital, where they were followed due to confirmed or suspicious hip dysplasia. They were between six to 10 months of chronological age at the time of the trial.

The extremely preterm born infants were born before gestational week 28+0 and had no periventricular leukomalacia (PVL) or any other major brain abnormalities. A diagnosis of retinopathy of prematurity led to exclusion. At this time, all extremely preterm born infants were also included in a study that performed brain MRI at term-equivalent age. To be able to use these MRI scannings, we did not include infants with any grade of PVL or IVH grade III and IV on neonatal ultrasound, focal brain lesions, such as cysts and malformations, persistent ventricular dilatation on MRI examination at term-equivalent age or qualitatively defined moderate or severe white matter abnormalities.

4.1.2 Study groups

The study discussed in Paper I comprised 27 children and for the study in Paper II, the full-term group was increased by another 11 infants, giving us 38 infants. Due to technical problems or artifacts, eight infants were excluded in Paper I and four were excluded in Paper II and no results were obtained from these infants. This means that the analyses were based on 26 infants. In Paper II, the preterm group comprised 33 infants, but six had to be removed from the analyses due to artifacts, resulting in 27 infants. For the MRI analyses, scans from 10 infants were of sufficient quality to be included in the analyses.

Table 4.1. Patient characteristics

	Preterm (n=27)	Full-term (n=26)
Sex male/female, n (% male)	14/13 (52)	13/13 (50)
Gestational age, mean weeks + days (±SD)	25+6 (1+0)	39+3 (1+4)
Birth weight, mean kg (±SD)	0.857 (0.118)	3.424 (0.614)
Age at trial, mean days (±SD)	241 (38)	216 (31)
Weight at trial, mean kg (±SD)	8.2 (1.2)	8.3 (1.1)

4.1.3 Procedure

The infants sat on their mothers' laps facing a computer screen that was approximately 50cm in front of them. The stimulus sequence started with a grey screen that was also used as a baseline, followed by the mother's face and an unknown face in random order, with a grey screen in between as a wash-out period. The pictures were presented for at least 15 seconds from when the infant focused their gaze on the screen. All trials were videotaped to help identify major movement artifacts. The infants in both studies were randomized into two groups. Group A comprised 28 infants who were exposed to their mother's face first and then the unknown face and the order was reversed for the 25 infants in Group B.

4.1.4 fNIRS methodology

In Paper I, we used the NIRO 300 fNIRS device and in Paper II we also used the successor NIRO 200 (Hamamatsu Photonics, Hamamatsu, Japan). Both of these devices were equipped with two channels. Four wavelengths of light (775, 810, 850, and 910 nm, respectively) were delivered by pulsed laser diodes and scattered light was detected by closely placed optodes. The emitting and receiving optodes were placed in a rubber holder with fix inter-optode distances of 4 or 5cm.

The optodes were fixed onto the infants' heads using an elastic hat or band-aid and the optode location was assured from landmarks using the 10-20 EEG system. One channel was located over the frontotemporal region and the other was placed over the occipital region, with both over the right hemisphere, which is known to be more involved in facial recognition than the left (Kanwisher et al. 1997) (Figure 4.1).

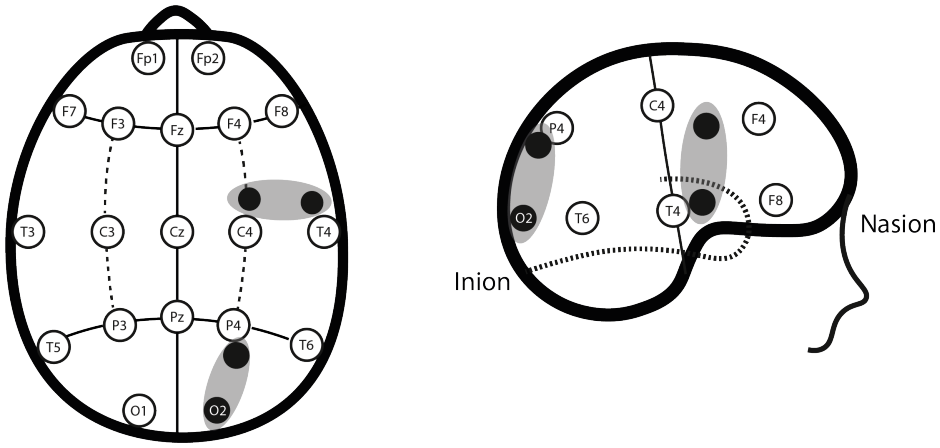

Figure 4.1. *Optode location in relation to the 10-20 EEG system.*

4.1.5 MRI methodology

All the extremely preterm-born infants in Paper II were scanned at term-equivalent age on a Philips Intera 1.5-T magnetic resonance imager (Philips International, Amsterdam, The Netherlands). The conventional MRI protocol consisted of a sagittal T1-weighted turbo spin echo sequence, an axial inversion recovery sequence and an axial T2-weighted sequence. The three-dimensional T1-weighted gradient echo images were acquired with an echo time of 4.6 minutes, a repetition time of 40 minutes, a flip angle of 30 degrees, a voxel size of 0.7 x 0.7 x 0.1 mm and a 180mm field of view. Details of the sequence parameters have previously been published (Skiold et al. 2012). T1-weighted images were assessed for quality assurance.

4.1.6 Statistics

We collected data in 2Hz and transferred it to a computer for further analysis. Relative changes in HbO_2 and HHb were calculated by the relevant NIRO device using a modified Beer-Lambert law. The videos were used to identify major movements related to artifacts in which the HbO_2 peaked briefly (<5 seconds and > 8 mmol/L) and artifact data were replaced using linear interpolation to enable us to attenuate single artifacts without losing data from the entire trial. For each stimulus, the mean value of the first 15 seconds when the infants looked at the screen was used in the analyses and this was compared to the mean of the 10-second baseline. Cortical activations were identified as significant increases in HbO_2. We performed ANOVA for repeated-measures analysis using mean values for each time point, to compare the different stimulus periods, and carried out a *post hoc* comparison using the Newman-Keuls method for comparisons between the cohorts, groups and stimuli within the cohorts and groups. In Paper II, we analyzed the hemodynamic response over time using ANOVA to compare the repeated measures for different stimuli. The data were rearranged from the randomized facial presentation order so that the data from the presentation of the mother's face were placed directly after the baseline, followed by the gray screen and the unknown face at the end to be able to show all data in a timeline. A P-value of <0.05 was considered to be statistically significant. The statistics were calculated using Statistica (StatSoft Inc., Tulsa, Oklahoma, USA).

Analyses of the MRI data include preprocessing of the T1-weighted images and reorientation and removal of non brain tissue components. Structural volumes were segmented into gray matter, white matter, cerebrospinal fluid, deep gray matter (basal ganglia and thalami), cerebellum, and brainstem, using the segment option of SPM version 8 (University College London, London, United Kingdom), running on MATLAB version 7.5 (MathWorks, Natick, Massachusetts). For guiding segmentation, we used tissue probability maps from preterm-born infants scanned at term-equivalent age (Kuklisova-Murgasova et al. 2011). The segmented brain tissues were spatially normalized using DARTEL (Ashburner 2007). Images were modulated and smoothed (3-mm Gaussian kernel). A simple regression was performed using voxel-based morphometry to test for possible relationships between regional gray matter volume and HbO_2 concentrations in the preterm-born group. We used an uncorrected threshold of $P < 0.005$ and only considered clusters that were larger than 10 voxels.

4.2 NOSOCOMIAL AND MATERNAL ODOR PERCEPTION, PAPERS III AND IV

4.2.1 Inclusion and exclusion criteria

Infants with major congenital abnormalities or brain injuries and infants who had received analgesics/sedatives during the last 48 hours before the test were not included.

4.2.2 Study groups

4.2.2.1 Paper III

We included 41 infants who underwent 44 recording sessions. They were divided into three groups with 15 infants in the very preterm group (born between 28-32 weeks of gestation), 12 in the very preterm infants at term-equivalent age group and 17 full-term born infants.

Table 4.2.1. Patient characteristics

	Preterm n = 15	**Preterm at TEA n = 12**	**Full-term n = 17**
Gestational age at delivery (wks)	31 (28-32)	29 (25-31)	39 (38-41)
Birth weight (g)	1471 (±223)	1173 (±326)	3556 (±404)
Male/female ratio (n)	8/7	7/5	9/8
SGA/AGA ratio (n)	2/13	2/10	0/17
Duration of respiratory support (d)			
Mechanical ventilation	0 (0-3)	0 (0-4)	-
Nasal CPAP	3 (0-8)	3 (3-53)	-
At recordings			
Postnatal age (d)	8 (3-25)	79 (64-113)	2 (1-3)
Corrected age (wks)	32 (31-32)	40 (38-42)	40 (38-42)
Weight (g)	1464 (±205)	3239 (±549)	3485 (±396)

Results are expressed as means (±SD) or median (range)
SGA, small for gestational age; AGA, adequate for gestational age; CPAP, continuous positive airway pressure; TEA, term-equivalent age

4.2.2.2 Paper IV

Infants were included in three different groups depending on their gestational age at birth: 15 very preterm infants (born between week 28-32), 13 late preterm infants (born between week 33-37) and 17 full-term infants.

Table 4.2.2. Patient characteristics

	Very preterm n = 15	Late preterm n=13	Full-term n = 17
Gestational age at delivery (wks)	31 (28-32)	34 (33-36)	39 (38-41)
Birth weight (g)	1471 (±223)	2175 (±402)	3556 (±404)
Male/female ratio (n)	8/7	11/2	9/8
SGA/AGA ratio (n)	2/13	2/11	0/17
Duration of respiratory support (d)			
Mechanical ventilation	0 (0-3)	0 (0-1)	-
Nasal CPAP	3 (0-8)	0,5 (0-4)	-
At recordings			
Postnatal age (d)	8 (3-25)	5 (2-25)	2 (1-3)
Corrected age (wks)	32 (31-32)	35 (34-37)	40 (38-42)
Weight (g)	1464 (±205)	2102 (±357)	3485 (±396)

Results are expressed as means (±SD) or median (range)
SGA, small for gestational age; AGA, adequate for gestational age; CPAP, continuous positive airway pressure.

4.2.3 Odors

4.2.3.1 Paper III:

We selected two odors with potential trigeminal properties that were commonly used in the NICU and in close proximity to the infants: a hand cleaner called DES IPA 60 (Lahega Kemi AB, Helsingborg, Sweden) and an adhesive remover called Convacare (Convatec, Deeside, UK). Convacare is used in its pure form for infant care and this was the way we chose to present it to the infants in the study. However, when the hand cleaner is used, staff are advised to consider the drying time of the solution so that the infant's exposure to the volatile alcoholic compound is reduced (Hsieh et al. 2018). Despite this, this advice is often forgotten or ignored during clinical routines, due to stress or lack of awareness. Therefore, we used both a diluted and pure solution of the hand cleaner. Water was used as an odorless control.

We used adult panels to chose which of the six distilled-water diluted solutions of hand cleaner (diluted to 1/2, 1/4, 1/6, 1/8, 1/16, 1/32) best matched the intensity of the odor released by the hands when they were washed in hand cleaner and left to dry for the recommended drying time of 30 seconds. The dilution to 1/6 was the best match and this was the one used for the hand cleaner test.

The adult panel also rated the intensity and irritation of the three odors and the odorless control, by using a visual analogue scale ranging from 0 (no intensity, no irritation) to 10 (highly intense, highly irritating). They also evaluated the pleasantness and unpleasantness of the odorous substances using another visual analogue scale ranging from -5 (very unpleasant) to +5 (very pleasant), with zero indicating a hedonically neutral perception.

The results of these evaluations are presented in Figure 4.2. The intensity, irritation and pleasantness of all the odors and the distilled water were judged to be significantly different. All the three odors were perceived as intense to very intense (mean values > 6.5). Only the

pure hand rub and diluted hand rub odors were perceived to be very irritating (mean values > 7.5), whereas the adhesive remover and water were perceived to be not irritating or slightly irritating (mean values < 2.5). The pleasantness of all the odors and the distilled water were judged to be significantly different. Only the pure hand rub and diluted hand rub were perceived as unpleasant, whereas the adhesive remover and water were perceived as pleasant.

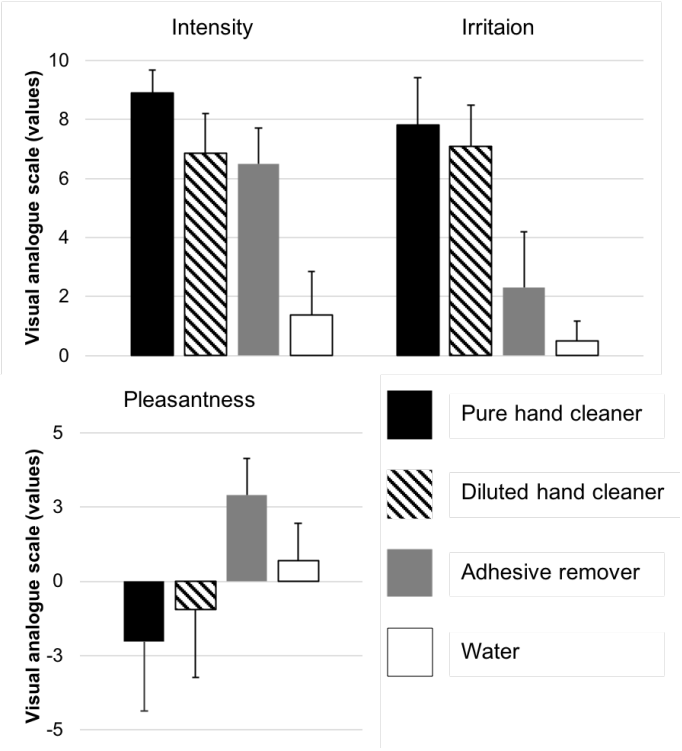

Figure 4.2. *Visual analogue scales for intensity, irritation and pleasantness for the odorous substances. Bars represent mean values and whiskers SD.*

4.2.3.2 Paper IV:

The MBO was presented to the infants using the same routine as in the clinic. The odors were collected during the night before the test by the mother wearing a cotton cloth close to her breast for 12 hours. The cloth was then stored in a glass jar to preserve the odor quality. A clean cloth washed in an unfragranced product was used as a control. To identify whether the odors had intense, irritating and pleasant natures, an adult panel was convened before the study started. Odors from six different mothers were used and compared to two control odors. The panel consisted of 29 non-smoking healthcare and laboratory staff, with a mean age of 26 years. There were no statistical differences in how the raters judged the three parameters between the MBOs and the control, but some MBOs were rated as significantly more intense and more irritating than others. The control odors were rated as similar for all properties. On a visual analogue scale ranging from 0-10, both the intensity and irritation for all MBOs were rated as low, with a score of 0-2. The MBOs were judged to be hedonically neutral.

4.2.4 Procedure

The infants in both studies were tested in their open bed or incubator in a separate, quiet, well-ventilated room with dimmed light 30 minutes after feeding. We randomly presented the odors 1cm below their noses. In the study reported in Paper III we used a 20cm long cotton bud soaked in the solutions and in the study reported in paper IV, the cotton cloths were held using 18cm long forceps to avoid exposure to the odor of the presenter's hand. The infants were in an active sleep state during the presentations. The duration of the presentation was 10 seconds in both studies and there was a minimum of two minutes between presentations.

In Paper III, after all odors had been presented once, pure hand cleaner, adhesive remover and water were presented again, two minutes after oral glucose of 0.25 ml had been administered. Physiological data, such as heart rate, oxygen saturation and breathing frequency, were also recorded during the trials and the infant's behavior was videotaped. Two nurses unaware of the study purpose, and blinded to the nature of the odors, analyzed the videos to evaluate them for pain, using a modified version of the well-validated neonatal facial coding system (NFCS) (Grunau et al. 1998).

4.2.5 fNIRS methodology

We used the NIRScout (NIRx Medizintechnik GmbH, Berlin, Germany), which has eight sequentially switched emitters and four receivers, providing eight different channels. The sampling rate was 6.25 Hz, and the wavelengths of NIR light were 760 nm and 850 nm. The optodes were fixed in elastic caps, which were individually fitted depending on the infant's head circumference and pre-marked with the help of the 10-20 EEG system. Six different caps were used, with head circumferences ranging from 26-36 cm and IODs from 2.5-4 cm. This allowed us to explore the olfactory networks in infants of different ages and head sizes. The optodes were placed over areas known to be involved in olfactory and trigeminal processing, such as the olfactory cortex and frontal cortex (FC). In Paper III, hemodynamic changes in the somatosensory cortices (SC), with two channels over each hemisphere, SCa, and SCb, were also measured.

4.2.6 Statistics

The time window for analysis was 0-30 seconds after the onset of the stimulus, to record the range of maximum concentration changes from baseline (-10 seconds to 0 seconds). We developed a rigorous process for artifact identification, validation and suppression that was based on previous recommendations. In summary, we visually identified spikes in HbO_2 of more than five μmol from the previously recorded value where HbO_2 and HHb changed in unison. We also identified changes in the threshold value of 20 μmol in HbO_2 from baseline, based on the calculation of the standard deviations of the whole datasets. Quantitative changes over time were assessed using ANOVA for repeated measures for the entire time window (-10 to 30 seconds), with the Newman-Keuls *post hoc* test when appropriate. Comparisons between odors and groups of infants were performed using one-way ANOVA. In Paper III, mean changes in pain scores were evaluated for 10-second periods and

comparisons to baseline and other odors were calculated using ANOVA for repeated measures. A P-value below 0.05 was considered statistically significant. Cortical activation in a specific area was identified as statistically significant, based on ANOVA of HbO_2 variations relative to baseline, if the values increased, and if HHb was, at least, stable or showed a simultaneous decrease.

5 RESULTS AND DISCUSSION

The most important results and discussion points are presented in this part. For complete results for all studies, see the published papers and manuscript.

5.1 FACIAL RECOGNITION, PAPERS I AND II

In both Papers I and II, we found that full-term born infants had a larger hemodynamic response in the frontotemporal area during the presentation of the mother's face than while watching an unknown face. In Figure 5.1.1 we present a typical behavioral expression to the two different stimuli.

Figure 5.1.1 *An infant watching an unknown face (left) and his mother's face (right).*

In Paper I, cortical activation of the right frontotemporal area, measured as an increase in HbO_2 in relation to baseline following exposure to the maternal image, was larger than for the unknown image (Figure 5.1.2). This finding was independent of the facial image sequence order.

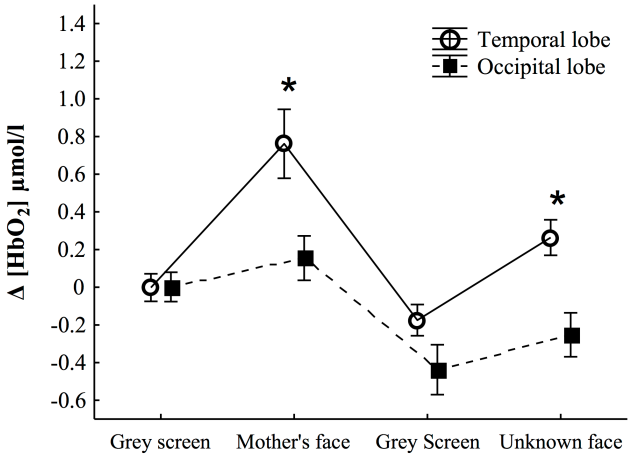

Figure 5.1.2. *Mean values of HbO_2 changes in the right frontotemporal area (circles) and occipital areas (squares) for all children. Exposure to both the maternal and unknown facial images elicited significant HbO_2 increases in the frontotemporal area. Vertical bars denote 0.95 confidence intervals, and stars denote significant changes in relation to baseline ($p<0.001$).*

In the study reported in Paper II, we found cortical activation in the frontotemporal cortex in the full-term group during the exposure to the mother's face and this activation was identified as significant based on ANOVA of HbO_2 variations compared to baseline. These findings were similar to those reported in Paper I. The unknown face elicited no significant cortical activations. In Paper II, we also included 27 extremely preterm born infants, investigated at six to 10 months of corrected age. In this group, we found no significant HbO_2 variations during any stimulation. In Figure 5.1.3 the hemodynamic response curves for both groups are presented.

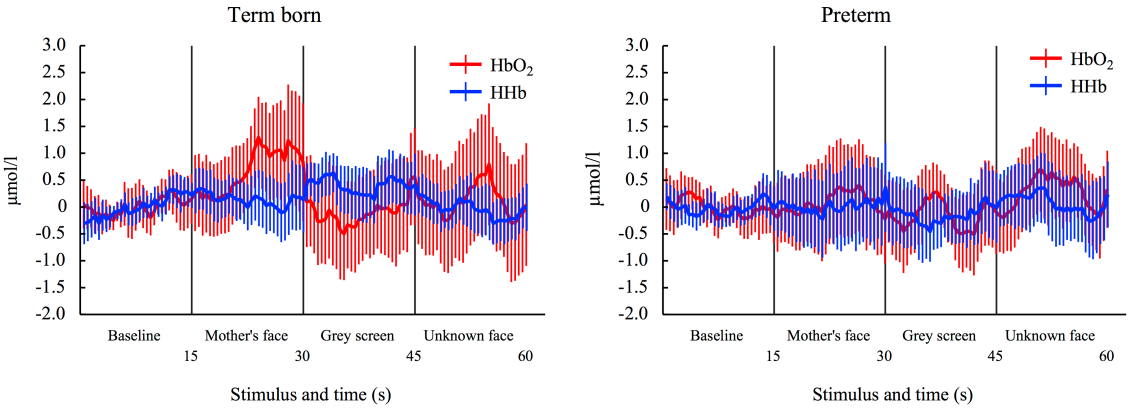

Figure 5.1.3. *In the term-born infants (left graph), the mothers' faces elicited a significant increase in HbO_2 in the right frontotemporal area. A typical activation pattern is seen, with a simultaneous increase of HbO2 and a decrease or stabilization of HHb. There were no significant differences of HbO_2 in the preterm-born group (right graph). Vertical bars denote 95% confidence intervals.*

The study reported in Paper II allowed us to compare the cortical hemodynamic responses between the two groups of infants. Relative changes in HbO_2 were averaged over each stimulation period and compared using ANOVA for repeated measures. Comparison of the two groups revealed a higher amplitude HbO_2 increase in the right frontotemporal area in the term-born infants than the preterm-born group when seeing the mother's face and a significantly smaller mean HbO_2 increase when presented with the unknown face (Figure 5.1.4). The within-group comparisons showed that term-born infants displayed a significantly higher amplitude response to their mothers' faces than to the unknown faces. In contrast, the preterm-born infants displayed a significantly smaller amplitude response to their mothers' faces than to the unknown face.

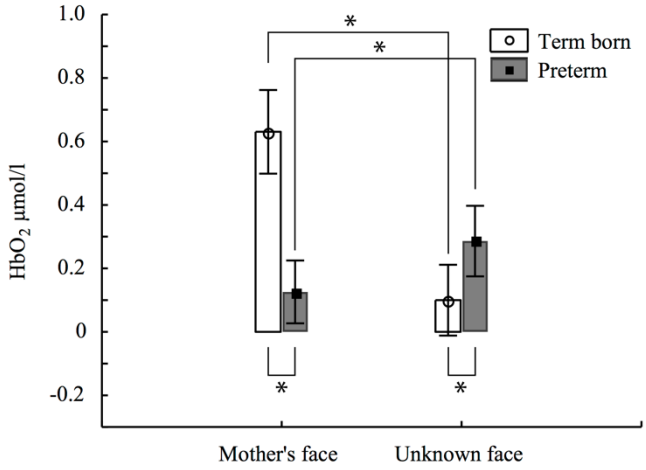

Figure 5.1.4. *The difference in mean values of HbO_2 to baseline in the right frontotemporal area. In the preterm-born group, both facial presentations elicited a significant increase of HbO_2 in the right frontotemporal area compared to baseline, but the unknown face elicited a larger response than the mother's face. In the term-born cohort, the image of the mother's face elicited a significantly higher response than the image of the unknown face and a significantly larger increase in HbO_2 than the preterm-born cohort. Vertical bars denote 95% confidence intervals, and asterisks indicate $P < 0.001$.*

We also measured hemodynamic changes in the occipital lobe in both groups and the only significant increase in HbO_2 occurred when the term-born infants viewed their mothers' faces.

In each group of infants, we could also analyze the effect of presentation order. The groups were divided into two different groups - A and B - depending on the presentation order. The term-born infants included in Paper II demonstrated a significantly higher increase in HbO_2 following the presentation of their mothers' faces compared with the unknown face, independent of the order of presentation (Figure 6.1.5). The same response profile was found in Paper I, but the amplitudes of the hemodynamic responses were slightly different. The preterm-born infants demonstrated a significantly larger HbO_2 increase to the first face presented compared with the second, regardless of whether it was their mother or the unknown face (Figure 5.1.5).

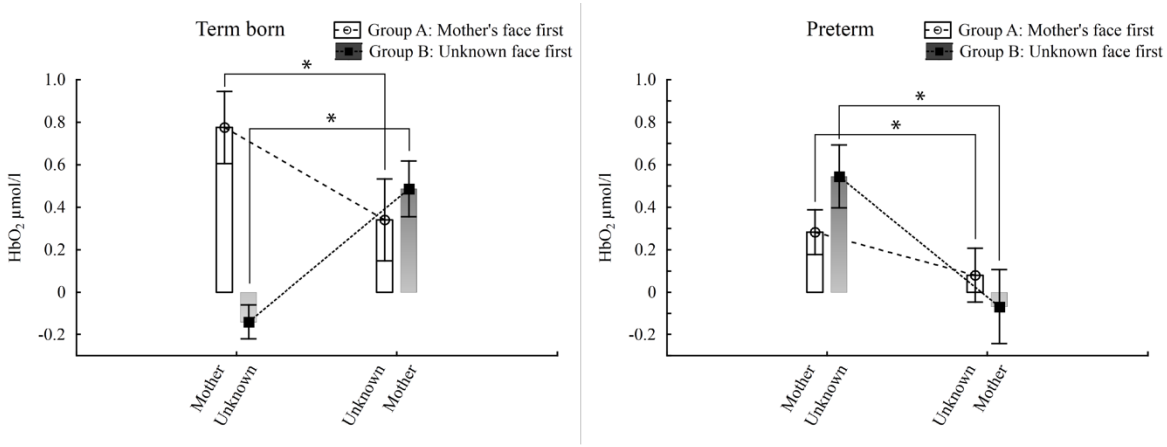

Figure 5.1.5. *The mother's face elicited a significantly larger HbO_2 increase than the unknown face, independent of the presentation order for term-born infants (left graph). The first facial image presented elicited a significantly larger HbO_2 increase, independent of familiarity, for preterm-born infants (right graph). *P < 0.001.*

In Paper II we also correlated the functional hemodynamic responses of the preterm infants to regional brain volumes. A simple regression analysis using voxel-based morphometry revealed a negative correlation between HbO_2 during the unknown face presentation and the regional volume of the left fusiform gyrus and left amygdala in the preterm-born infants (Figure 5.1.6). There was no correlation between HbO_2 and cortical volume during the presentation of the mothers' faces.

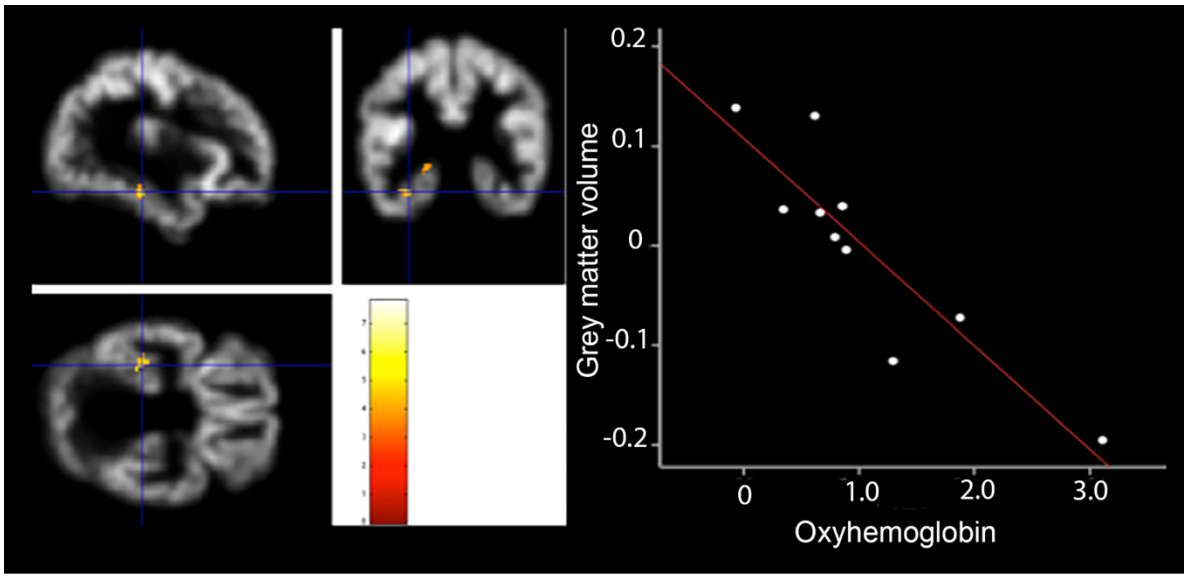

Figure 5.1.6. *Correlation between gray matter involving the left fusiform, amygdala and temporal HbO_2. Plot points indicate real data on the maxima corresponding to the fusiform gyrus. The line indicates data adjusted to the theoretical model.*

5.1.1 Discussion

The main finding of these studies was that infants who were born extremely preterm displayed different functional cortical activation when they looked at known and unknown

faces at a corrected age of six to ten months, compared to term-born infants at six to ten months. The preterm born infants showed a significantly smaller hemodynamic response in the right frontotemporal areas while watching their own mother's face than the term-born infants. In the term-born group, the image of the mother's face elicited a significantly higher hemodynamic response than the image of an unknown face. We also found that when an unknown face was presented to the preterm infants, they displayed a negative correlation between HbO_2 and regional grey matter volumes in the fusiform gyrus and amygdala. These findings could be early signs of impaired facial recognition, in line with the fact that extremely preterm infants are more prone to developing prosopagnosia, the inability to recognize faces, later in life.

5.1.1.1 Brain injuries or altered sensory input?

The difference in cortical activation between preterm and full-term born infants were in line with reported functional and clinical data. The hemodynamic effects we found could have been a result of brain injuries or an altered sensory input during the critical weeks of brain maturation in the preterm born infants. Neonatal morbidities, such as PVL and bronchopulmonary dysplasia (BPD), are known risk factors for developing prosopagnosia in preterm infants (Fazzi et al. 2009, Potharst et al. 2013). The infants in our study did not have PVL, but 11 of the 27 preterm infants had moderate to severe BPD and required oxygen support at 36 weeks of postmenstrual age. Preterm infants with low birth weights scored worse on a face recognition task at eight years of age (Perez-Roche et al. 2017). However, these infants were not born extremely preterm. In our group of infants, virtually all of them had an appropriate weight for their gestational age at birth and it was not possible to perform a sub-analysis. IVH and patent ductus arteriosus (PDA) ligation were correlated with reduced brain growth in a previous study from our co-author (Padilla et al. 2014). Of the 10 infants that we included in the MRI analysis, one had undergone PDA ligation and three had IVH: two had grade 1 and one had grade 2.

Preterm infants are more likely to suffer from other social and neurodevelopmental disorders, such as ASD and CVI (Dutton and Jacobson 2001, Johnson and Marlow 2011, Lampi et al. 2012, Geldof et al. 2015). Padilla et al. also found that extremely preterm infants who tested positive for ASD at 6.5 years of age had reduced brain volumes at term and that the infants with ASD had a higher frequency of neonatal morbidities (Padilla et al. 2017). When children have ASD, the early disruption of the amygdala function by congenital or acquired lesions, or by genetic anomalies, can result in atypical development of the network of regions involved in the processing of social stimuli (Johnson 2005). CVI could be partly due to ventral stream dysfunction and the difficulties in recognizing faces could be due to a lesion in the temporal lobes. Preterm infants can also have a dysfunctional dorsal stream, which is more involved in spatial location and motion perception. One study found that visual tracking capabilities at four months of age could predict the infant's neurodevelopmental outcome at three years of age (Kaul et al. 2016).

Infants who are born preterm have a longer extra uterine experience to visual stimuli and probably facial stimuli, due to the high turnover of medical staff, than healthy infants born at term. Sensory input, in terms of both a lack of sensory input and overstimulation during the first weeks of life, can have long-term consequences on the size and function of the brain. In addition to reduced global and regional cortical grey matter, Padilla et al. also showed that infants born extremely preterm had increased volumes of cortical grey and white matter in the regions involved in visual processing when they were examined at term (Padilla et al. 2014). How this affects the functional circuits is not yet known, but rat pups who were over-stimulated with specific sound frequencies had enlarged cortical areas near that tone, but impaired perceptual discrimination of the over-represented frequencies (Han et al. 2007). It has also been reported that infants with congenital cataracts were impaired when it came to certain aspects of face processing, indicating that early deprivation can affect later facial recognition abilities (Le Grand et al. 2001). Altered sensory input during the critical neonatal period could partly explain our findings.

5.1.1.2 Correlations between functional and anatomical data

The negative correlation between regional volumes in the fusiform gyrus and amygdala and the hemodynamic response to an unknown face in preterm born infants is very interesting. These findings were not hypothesis-driven, but they were the only areas with a correlation to HbO_2. That negative correlation might represent a mechanism that compensates for structural alterations in extremely preterm infants, as previously demonstrated (Padilla et al. 2014). It may be that regions with some kind of atrophy need additional amounts of HbO_2 in order to react. The atrophic areas may also need to recruit additional brain areas when performing a difficult task that exceeds the resources of those particular regions, as previously described by Lawrence et al. (Lawrence et al. 2014). In addition, facial perception is a process that is supported by distributed cortical and subcortical networks, where the different parts of each network interact with each other. In this regard, the amygdala, the fusiform gyrus and the temporal and prefrontal cortices form an interconnected system that is involved in representing different aspects of faces (Adolphs 2003). This could explain the correlations between HbO_2 values, detected by the frontotemporal fNIRS channel, and amygdala and fusiform gyrus volumes in the context of facial recognition. The fNIRS optodes in this study covered a large area of the frontotemporal lobe and the HbO_2 is the sum of the whole area, with some of the increased HbO_2 resulting from activation in these additional areas.

Since the amygdala is a crucial region in processing emotions and aspects of familiarity in recognizing memories (Farovik et al. 2011), we could speculate that the negative correlation between the amygdala volume and magnitude of the HbO_2 response in preterm infants could represent the emotional component related to the fact that they found a stranger's face unfamiliar. Nevertheless, we did not measure any physiological parameters that would have supported a reaction of fear or unfamiliarity.

5.2 NOSOCOMIAL AND MATERNAL ODORS, PAPERS III AND IV

5.2.1 Nosocomial odors and pain, Paper III

We analyzed the hemodynamic odor responses of all infants, together and in subgroups. As expected, exposure to water led to no hemodynamic changes. In all infants, pure hand cleaner and diluted hand cleaner elicited significant cortical activations in all nociceptive areas (somatosensory cortices) and in at least two of the four olfactory areas (olfactory or frontal cortices). Adhesive remover elicited a significant cortical activation in one nociceptive area and tended to activate one olfactory area.

In all full-term and preterm infants, there were significant cortical activations in at least one olfactory and one nociceptive area to at least one odor. The full-term infants responded with bilateral cortical activation in only the nociceptive areas following exposure to pure hand cleaner and to diluted hand cleaner in both the olfactory and nociceptive areas. After the exposure to pure hand cleaner, the very preterm infants responded with cortical activation in just one nociceptive area. Diluted hand cleaner led to cortical activation in one olfactory and one nociceptive area and adhesive remover to bilateral responses in olfactory and nociceptive areas. At term-equivalent age the very preterm infants responded to pure and diluted hand cleaner with cortical activation in the olfactory areas. Diluted hand cleaner led to bidirectional hemodynamic changes in HbO_2 in the nociceptive areas, namely increases and decreases, and ANOVA showed that these changes were statistically significant. However, it was not possible to identify the direction of the changes, due to no significance in a *post hoc* test. Adhesive remover triggered cortical activation in the nociceptive and olfactory areas. Table 6.2 shows all the cortical activations to all of the odors by all of the groups.

Table 6.2: Cortical activations in subgroups

Channel Location	Pure hand cleaner		Diluted hand cleaner		Adhesive remover	
	ANOVA	P-value (post hoc)	ANOVA	P-value (post hoc)	ANOVA	P-value (post hoc)
Very preterm (n=15)						
OC Left	-		-		↑ P<0.001	-
OC Right	-		-		-	
FC Left	-		↑ P=0.006	-	↑ P<0.001	-
FC Right	-		-		↑ P<0.001	-
SCa Left	-		-		↑ P<0.001	-
SCa Right	↑ P=0.002	0.05	↑ P<0.001	-	↑ P<0.001	-
SCb Left	-		-		-	
SCb Right	-		-		↑ P<0.001	-
Full-term (n=17)						
OC Left	-		↑ P<0.001	-	-	-
OC Right	P=0.059		-		-	-
FC Left	-		↑ P<0.001	-	-	-
FC Right	-		↑ P=0.001	-	-	-
SCa Left	↑ P<0.001	0.03	↑ P=0.015	-	P=0.09	-
SCa Right	↑ P<0.001	-	↑ P<0.001	<0.001	P=0.06	-
SCb Left	↑ P<0.001	0.002	↑ P<0.001	-	-	-
SCb Right	↑ P<0.001	0.02	↑ P<0.001	-	-	-
Very preterm at term-equivalent age (n=12)						
OC Left	↑ P=0.01		↑ P=0.03		↑ P<0.001	-
OC Right	↑ P=0.04		-		↑ P<0.001	-
FC Left	-		-		↑ P=0.02	-
FC Right	↑ P<0.001	0.001	-		↑ P<0.001	0.01
SCa Left	0.06		↓↑ P=0.02	-	↑ P<0.001	-
SCa Right	-		↓↑ P<0.001	-	-	
SCb Left	-		-		-	
SCb Right	-		-		↑ P=0.001	-

Note: ↓↑ *arrows indicate the direction of the observed variations and the associated P-values indicate statistical significance (ANOVA for repeated measures). If there was a bidirectional hemodynamic change, and if there were no significant post hoc analysis, it was impossible to decide the direction of the significant ANOVA. In those cases, a double arrow was used. Olfactory cortex (OC), Frontal cortex (FC), Somatosensory cortex (SC).*

The inter-rater agreement in the assessment of pain behavior was 91.8% and Cohen's kappa was 0.52. All three odors elicited significantly higher NFCS scores than water in all of the presentation and post-presentation periods. When we compared the maximum NFCS values during the 40-second post-stimulus period to the baseline results, these indicated that all the odors elicited a significantly increased NFCS score. The maximum values were significantly

higher for pure hand cleaner and diluted hand cleaner than for adhesive remover, but were similar for pure and diluted hand cleaner. We calculated the average of the maximum NFCS values for all odors for each infant and compared them between the groups. We found no significant differences in the pain behavior between groups.

Pearson correlation analysis indicated no significant correlations between the maximum NFCS scores and the maximum HbO_2 for any odor. We also compared HbO_2 changes in nociceptive areas following exposure to pure hand cleaner between two subgroups of infants: one group with a maximal NFCS score of 0-1 (no pain behavior) and another group with a maximal NFCS score of 2-4 (significant pain behavior). Infants with higher NFCS scores had significantly higher HbO_2 values in all nociceptive areas: mean of SCa left, SCa right, SCb left and SCb right (see Figure 5, Paper III). In addition, infants with higher NFCS scores had significant cortical activation from baseline in all nociceptive areas, but infants with lower NFCS scores had no significant hemodynamic changes in these areas.

For all infants, administering oral glucose before they were exposed to pure hand cleaner suppressed cortical activation in SCa bilaterally. More specifically, the hemodynamic response to pure hand cleaner in SCa (left and right merged) was significantly different for infants who did and did not receive glucose (see Figure 7a, Paper III).

We also observed differences in the effect of glucose among the three major groups. In full-term and very preterm infants, glucose suppressed cortical activations in SCa following exposure to pure hand cleaner. Moreover, full-term infants who did and did not receive glucose had significantly different cortical activation following pure hand cleaner in SCa (left and right merged) (see Figure 7b, Paper III). In the very preterm infants tested at term-equivalent age, who had no cortical activation in response to just pure hand cleaner, odor exposure after glucose administration triggered significant cortical activations. However, in this group, glucose suppressed the cortical activations in SCa following exposure to adhesive remover.

There were significantly lower NFCS scores for all infants in response to pure hand cleaner if they were given glucose before odor presentation (see Figure 7c, Paper III). This regimen also affected the NFCS scores in full-term infants (see Figure 7d, Paper III). For the very preterm and very preterm infants at term-equivalent age, glucose did not alter the NFCS scores after exposure to pure hand cleaner. However, when the very preterm infants at term-equivalent age were exposed to adhesive remover, their scores were lower when glucose was administered. Oral glucose altered the hemodynamic and behavioral responses in all groups. It also led to significant differences in the profiles of the hemodynamic changes in at least one nociceptive area and for at least one odor in all three groups. However, the effect of glucose was not consistently present for all odors in all groups.

5.2.2 Maternal odors, Paper IV

In the full-term infants, the MBO scent elicited significant cortical activations in the olfactory cortices bilaterally and in the left frontal cortex. The control stimulus did not affect the olfactory cortices, although it affected the frontal cortex bilaterally.

In the late preterm group, we found cortical activation in the right olfactory cortices following the exposure to MBO and the control odor elicited cortical activation in the left olfactory cortices and the right frontal cortex.

The very preterm group displayed no cortical activation with either the MBO cloth or the control cloth washed with a fragrance-free product.

Activations in the olfactory cortices are presented in Figure 6.2, and Table 6.6.2 presents the cortical activations in all areas for all three groups.

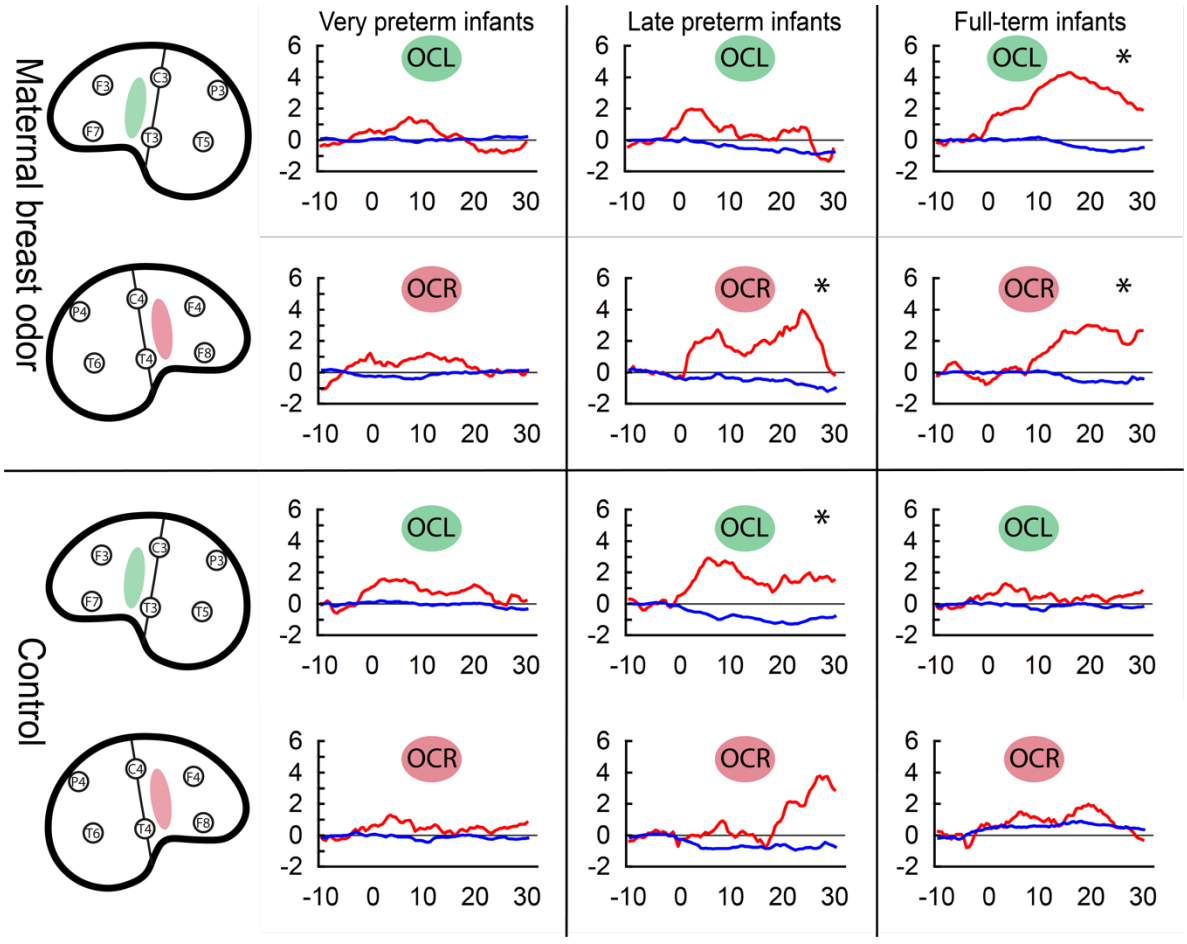

Figure 2: *Haemodynamic changes following exposure to maternal breast odor and the control odor in all groups and all brain areas, with HbO_2 in red and HHb in blue in µmol/L vs time in seconds. The two upper lines represent activation in the olfactory cortices after exposure to MBO and the two bottom lines after exposure to the control odor. A star indicates a statistically significant cortical activation ($P<0.05$).*

Table 6.2.2: Cortical activations in all groups

Location	Maternal breast odor		Control	
	ANOVA	P-value (post hoc)	ANOVA	P-value (post hoc)
VPT (n=15)				
OC-Left	-		-	
OC-Right	-		-	
FC-Left	-		-	
FC-Right	-		-	
LPT (n=13)				
OC-Left	-		↑ P<0.001	-
OC-Right	↑ P<0.001	-	-	
FC-Left	-		-	
FC-Right	-		↑ P<0.001	0.01
FT (n=17)				
OC-Left	↑ P<0.001	0.02	-	
OC-Right	↑ P<0.001	-	-	
FC-Left	↑ P<0.001	-	↑ P=0.03	-
FC-Right	-	-	↑ P=0.02	-

Note: ↑ *arrows indicate the direction of the observed variations and the associated p-values indicate statistical significance (ANOVA for repeated measures). Post hoc was calculated using Newman-Keuls. Olfactory cortex (OC), frontal cortex (FC).*

When we looked at all the subjects, we noted that both sexes demonstrated cortical activation in the olfactory cortices following exposure to the MBO, but this only occurred unilaterally in the girls. Full-term boys and girls showed bilateral activation of their olfactory cortices, while very preterm boys showed unilateral activation. There was no activation in preterm girls. There was insufficient power to perform a gender analysis in the late preterm born infants due to an unequal distribution of gender.

5.2.3 Discussion nosocomial and maternal odors

Our main findings were that nosocomial odors elicited not just olfactory responses but also nociceptive cortical responses and maternal odors elicited cortical olfactory responses, in full-term and very preterm newborns. As hypothesized, irritating nosocomial odors also elicited behavioral pain responses in very preterm and full-term infants, measured with the NFCS scale. We also found that oral glucose modulated trigeminal pain and significantly decreased hemodynamic cortical activation and pain behavior in full-term and very preterm infants. Finally, we observed differences in these responses between very preterm and full-term newborn infants due to brain maturation and the duration of the postnatal experience.

5.2.3.1 Cortical activations

In our studies, we used a clinically relevant and careful design that provided the infants with short odor exposures during active sleep. We protected the infants from other sensory modalities or odors that could have affected the outcome. The newborn infants that we included were divided into well-defined age groups so that we could assess the maturation of olfactory processing. Our results show that the olfactory and nociceptive cortical responses, which are probably mediated by the olfactory and trigeminal nerves, were present from 31 weeks of postmenstrual age, which was earlier than previously reported for olfaction (Bartocci et al. 2001). Our results also confirm the ability of very preterm, late preterm and full-term newborns to detect different components of odors (Sarnat 1978, Marlier et al. 2001, Schaal et al. 2004, Marlier et al. 2007), because their cortical responses varied according to the type of odor. The cortical processing of a low concentration of ecological odors by newborn infants adds a new dimension to published data that has demonstrated that infants display behavioral and physiological responses to their mother's scent (Sarnat 1978, Varendi et al. 1997, Varendi and Porter 2001, Raimbault et al. 2007, Doucet et al. 2009). The cortical activation demonstrated in our studies were in line with published data that showed olfactory cortical activation using fMRI when full-term newborn infants were exposed to formula milk and new artificial odors (Arichi et al. 2013, Adam-Darque et al. 2017). Adam-Darque et al. used eucalyptol, an odor known to have both olfactory and trigeminal properties, but they did not find any nociceptive cortical response after this stimulus, probably because of the low concentration of the odor they presented. To reach a full understanding of the developing neurological pathways involved in trigeminal, olfactory, and emotional processing, it is best to use composite measures such as fMRI, event-related potentials, high-resolution fNIRS or MEG combined with behavioral observations (Fitzgerald 2015). We attempted to use a multimodal approach in Paper III, by combining behavioral and cortical hemodynamic measurements, although we did not evaluate deeper brain structures that were not reachable by fNIRS.

In Paper III, hand cleaners elicited an almost pure trigeminal response, while, in contrast, the adhesive remover elicited a more bimodal olfactory/trigeminal response. This further supports our conclusion that infants can perceive these odors and react differently to them. The olfactory and trigeminal systems are connected and interact at several sites, including the nasal mucosa and the olfactory bulb (Hummel and Livermore 2002, Hummel et al. 2007, Hummel et al. 2009). Specific brain activation occurs in adults following trigeminal intranasal stimuli, in particular in the somatosensory cortices (Peyron et al. 2000, Apkarian et al. 2005, Hummel et al. 2009). In infants, olfactory/trigeminal and pain signals, and their emotional components, are also processed in deeper structures, although the amygdala and orbitofrontal cortex are activated to a lesser extent (Fitzgerald 2015, Goksan et al. 2015, Jin et al. 2015). However, the activity of the amygdala is hardly detected by the fNIRS signal.

We observed cortical activation in the somatosensory cortex, which supports the argument for pain processing that has previously been demonstrated in preterm infants with a mean postmenstrual age of 31 weeks (Bartocci et al. 2006) and at 25 weeks of postmenstrual age

(Slater et al. 2006). However, we cannot exclude that these hemodynamic changes were partially related to the facial motor responses accompanying pain behavior, due to the proximity between the motor cortex and SCa. Nevertheless, the differences in the maximum amplitudes of the HbO_2 changes that we observed between the groups were not associated with the differences in facial activity measured by the NFCS score. We also recorded cortical activation in SCb, which is a greater distance from the motor cortex. We observed high amplitudes in HbO_2 responses in accordance with previous recordings of neuronal activations in preterm infants (Bartocci et al. 2001, Bartocci et al. 2006, Slater et al. 2006, Olsson et al. 2016) following olfactory and nociceptive stimuli. Our cautious artifact removal process, and the opposite direction of the changes observed in HbO_2 and HHb following stimulus presentation, support neuronal responses rather than systemic responses (Yamada et al. 2012). Recently, additional measurements have been suggested to better identify systemic interference that could be useful in entirely excluding that possibility in the future (Caldwell et al. 2016).

5.2.3.2 Odor discrimination

In Paper III, the adult panel rated the odors as different in intensity and in paper IV they rated the MBO and the control as similar in intensity. The subjective differences in odor intensity in Paper III could have contributed to the variations in cortical responses and the similarities in odor intensity in Paper IV could explain why the control odor also elicited cortical activation in the olfactory areas. A sterile pad may have provided a better control as our control cloth could have retained some of the smell from the washing procedure, even though the product claimed to be fragrance free. However, the responses by the late preterm and full-term infants suggested that they can discriminate between different odors. Varendi et al. found that infants were able to discriminate between MBOs and other odors and they crawled towards MBOs (Varendi et al. 1997, Varendi and Porter 2001). The pleasantness or unpleasantness of odors may also affect the responses of preterm infants (Marlier et al. 2001, Goubet et al. 2003, Marlier et al. 2005). Thus, the different cortical responses that we observed for different odors could also have been due to differences in their hedonic value (Kringelbach and Berridge 2010).

5.2.3.3 Developmental changes

We found changes in trigeminal/olfactory processing with brain maturation and postnatal experience. Full-term infants had greater cortical responses in the somatosensory cortex following exposure to the stronger alien odors and in the olfactory cortex during exposure to MBOs. This was probably due to greater maturation of the nociceptive and olfactory neural pathways (Slater et al. 2006). However, when we compared full-term and preterm infants we used different IODs: all full-term infants wore a cap with a 4cm IOD, the late preterm infants wore caps with a 3-4 cm IOD and the very preterm infants wore a cap with a 2.5-3cm IOD. We are aware that the IOD can impact the depth of measurements and that an increase in IOD was possibly associated with a decrease in the signal to noise ratio. Our study design allowed

the exploration of the olfactory network involving deep brain structures in infants of different ages, head sizes and cortical volumes (Moeskops et al. 2015).

In Paper III, we also evaluated the impact of the postnatal experience by comparing the responses of very preterm infants at term-equivalent age and full-term infants. Full-term infants activated 11 of the 16 possible cortical areas after exposure to the odors with stronger trigeminal properties. Pure hand cleaner only activated the somatosensory areas, but diluted hand cleaner also activated the olfactory areas. Very preterm infants at term-equivalent age showed greater activation in the olfactory areas and less activation in the nociceptive areas. These differences could be due to habituation to trigeminal odors following repeated exposure. Habituation to olfactory stimuli is considered to be a simple form of non-associative learning, during which the response to non-relevant stimuli declines (Freedman et al. 2013). Research indicates that trigeminal and olfactory stimuli can induce habituation (Flohr et al. 2015). In the NICU, very preterm infants are not just exposed to strong odors from healthcare products, but also to air-jet induced trigeminal stimuli from respiratory devices, such as those that provide nasal continuous airway pressure. These stimuli could also play a role in the habituation process. Surprisingly, receiving oral glucose prior to the exposure to noxious odors increased cortical activation in the very preterm infants at term-equivalent age in contrast to the full-term infants. This could be because the very preterm infants had previous experience of oral glucose in the context of painful stimuli during their NICU stays. Indeed olfactory/trigeminal sensations can function as Pavlovian conditioners in humans (Moessnang et al. 2013).

5.2.3.4 Gender differences

In Paper IV, we reported that boys had more pronounced activation of their olfactory cortices than girls. In adults, most studies have shown that women outperformed men in odor detection and discrimination. However, functional studies have shown conflicting results, with higher cortical activation in men (Doty and Cameron 2009). Small studies have also shown gender differences in newborn infants, with girls turning their heads towards MBOs more often (Makin and Porter 1989). Thus, it is difficult to interpret our result or to put forward an explanatory hypothesis. We included a limited number of infants and the late preterm group was unevenly distributed by gender.

5.2.3.5 Pain behavior

The behavioral pain responses reported in Paper III after smelling irritating odors suggests that newborns can feel trigeminal induced pain or irritation before term, a response that has been well established in adults (Hummel et al. 2003). Exposure to the trigeminal stimuli that adults rated as stronger, namely hand cleaner, also led to higher pain scores in infants, suggesting a relationship between stimulus intensity and pain behavior. These findings indicate that the trigeminal pathways (Patel and Pinto 2014) seem to mature early in development (Hummel et al. 2007). Thus, different irritant chemical substances, including

alcohol, activate the intranasal nociception system, elicit trigeminal signals and trigger pain and irritation.

Researchers primarily developed the NFCS scale using the Baby FACS system (Ekman and Rosenberg 2005) to assess pain due to skin-breaking medical procedures (Grunau and Craig 1987). Facial expressions, especially those included in the NFCS scale, are the most specific indicators of pain in newborn infants (Holsti et al. 2005, Holsti et al. 2008). However, intranasal nociceptive stimulation might trigger less pain behavior than skin-breaking nociceptive stimulation (Rushforth and Levene 1994). Interestingly, we also observed associations between pain behaviors and hemodynamic changes in the somatosensory cortices. This provides a multimodal view of pain and suggests that newborn infants experience pain after exposure to trigeminal odors. Previous research has indicated discrepancies between pain behavior and cortical activation in the somatosensory cortex (Slater et al. 2008, Olsson et al. 2016). This suggests a possible dissociation between the sensory and affective elements of pain (Wilkinson et al. 2012).

5.2.3.6 Glucose modulation

Our finding that oral glucose can modulate pain and hemodynamic cortical activation supports the well-established use of oral glucose as pain relief for procedural pain in infants and adds evidence about the nociceptive brain activity (Stevens et al. 2016). We found that glucose modulated pain using a hemodynamic method, which was in contrast to Slater et al., who did not find a modulatory effect when they used a neurophysiological method (Slater et al. 2010). Trigeminal pain differs from the somatic pain that results from tissue-damaging stimuli and there may be different integration and modulation of these signals. Glucose, which is a pleasant gustatory stimulus, may be more effective in alleviating pain induced by other chemosensory stimuli, such as irritating odors with strong trigeminal properties, as previously reported in animals (Boucher et al. 2013). We can also speculate that sweet solutions may have a specific pain-relieving effect when the pain is from intranasal irritation. The mechanism by which sweet solutions modulate pain in newborn infants have not been fully elucidated (Holsti and Grunau 2010, Harrison et al. 2012). In animals, the hedonic value attributed to food, perceived through the ascending gustatory pathway, seems to play a prominent role in the analgesia that accompanies the ingestion of food (Foo and Mason 2009, Kringelbach and Berridge 2010). However, in human neonates, there is uncertainty about the role of the endogenous opioid system in the glucose-mediated alleviation of pain (Wilkinson et al. 2012). Some evidence suggests that the “analgesic” effect of glucose could be due to a gating mechanism (Leknes and Tracey 2008, Berridge and Kringelbach 2015).

5.2.3.7 Clinical implications

By the time they reach term-equivalent age, very preterm infants react to and cortically process alien odors differently to full-term infants. The number of painful and stressful procedures they undergo during neonatal life has been shown to have an impact on their brain growth and function (Smith et al. 2011), correlate negatively with intelligence quotients, be

associated with altered brain microstructures at seven years of age (Vinall et al. 2014) and have an impact on stress-sensitive behaviors (Ranger et al. 2014). Minimizing an infant's exposure to irritating odors during clinical procedures could be beneficial. Preterm infants have a lower pain threshold than full-term infants (Andrews and Fitzgerald 1994) and their pain experiences should be minimized. Thus, we recommend a more cautious use of the odorous healthcare products considered essential for infant care and for medical staff to be aware of the drying times of alcohol solutions when possible (Kuhn et al. 2011, Hsieh et al. 2018).

Cortical activation during exposure to MBOs adds a neurodevelopmental angle to the previously reported behavioral measures of early odor perception and support the clinical importance of MBO exposure for newborn infants. It also supports the practices of Kangaroo mother care and immediate skin-to-skin care. Kangaroo mother care has been proven to have long-lasting neuroprotective effects, with studies reporting higher intelligence quotients and fewer behavioral and social problems (Charpak et al. 2017). Maternal odor exposure during immediate skin-to-skin contact after delivery has been shown to improve the recognition and discrimination of the mother's milk odor (Mizuno et al. 2004). Preterm infants are commonly withheld from immediate skin-to-skin contact for medical reasons and this could affect their olfactory cortical networks. Exposure to MBOs during skin-to-skin contact has been shown to increase excited sounds in infants (Widstrom et al. 2011) and stimulate them to open their eyes (Doucet et al. 2007). This supports eye contact and maternal facial recognition by the infant and increases maternal oxytocin levels (Kim et al. 2014). All these mechanisms help to establish the attachment between mothers and their newborn infants.

As odors are processed in the developing cortex, atypical olfactory stimulation may interfere with the normal brain development and familiar odors may be able to play a neuroprotective role.

6 CONCLUSIONS AND FUTURE DIRECTIONS

Our findings suggest that the ability to recognize faces is defective in preterm born infants at a corrected age of six to ten months in comparison to term-born infants at the age of six to ten months. We believe that these studies will increase the awareness of prosopagnosia in this group of infants and hope that new methods can be found to follow and diagnose those at risk of this condition or other deficits in social perception.

We have also shown that very preterm infants develop trigeminal sensitivity before term-equivalent age, in that they cortically perceive alien odors from healthcare products. These nosocomial odors, with strong trigeminal properties, trigger the trigeminal pain system and induce pain behaviors and oral glucose reduces these responses. The differences between very preterm infants at term-equivalent age and full-term infants suggest that the NICU environment may affect the development of the chemosensory system. Preterm infants can also cortically perceive their mothers' breast odors. We hope that our findings will increase awareness about the newborn infant's capabilities to perceive odors among healthcare professionals and parents.

Longitudinal studies are needed to determine whether nosocomial and maternal stimuli influence future brain development in both positive or negative ways and to correlate early functional brain activity to future outcomes.

The mechanism by which glucose alleviates trigeminal pain warrants further research, which should also examine the mechanisms involved in trigeminal pain modulation.

Future studies should use composite measures of brain activity, behavior and clinical data to understand the developmental process better.

Depending on the research question and the infants' ages, fNIRS with high-density optodes could be used to be able to perform 3D mapping of brain activation.

7 SUMMARY IN SWEDISH

För tidigt födda barn som behandlas på neonatalavdelningar upplever andra sinnesintryck, som bearbetas i deras hjärnor som är under utveckling, än barn som fortsatt är kvar i livmodern. Dessa intryck kan påverka barnets framtida hjärnfunktioner och utveckling. För att förbättra vården av för tidigt födda barn och deras kognitiva utveckling behövs ökad förståelse kring vid vilka utvecklingsstadier som vilka funktioner i hjärnan kan aktiveras, och kunskap från detta behöver implementeras i vården och uppföljningsprogrammen. Hjärnans aktivitet som följer efter sinnesintryck kan mätas med funktionell near-infrared spectroscopy (fNIRS), en metod kan mäta förändringar i blodets syresättning i små områden med korta intervall. Denna avhandling syftar till att studera hur sinnesintryck från mammor och sjukhusmiljöer behandlas i hjärnbarken hos spädbarn.

I studie I studerade vi hur ett känt ansikte (barnets mamma) och ett okänt ansikte bearbetas i hjärnbarken när de var sex till tio månader gamla. Vi fann att barnen uppvisade hade en större aktivering av områden i hjärnbarken som bearbetar ansikten till igenkänning (främre tinningloben) när de tittade på sin mammas ansikte än när de tittade på det okända ansiktet.

I studie II jämförde vi lokala reaktioner i hjärnbarken på kända och okända ansikten mellan barn som var födda extremt mycket för tidigt (innan 28:e graviditetsveckan) och barn som var födda efter fullgången graviditet. Vi ville också korrelera hjärnreaktionerna med regionala hjärnvolymer. Spädbarnen undersöktes vid sex till tio månaders ålder med hjälp av fNIRS. I den för tidigt födda gruppen utförde vi också en hjärnavbildning med magnetresonanskamera. De för tidigt födda spädbarnen hade en lägre aktivitet i högra främre tinningloben medan de tittade på det kända ansiktet än de fullgångna barnen. Vi fann en negativ korrelation mellan hjärnaktiviteten och regionala volymer i hjärnbarken i områden som bearbetar ansikten (vänster gyrus fusiformis och amygdala).

I studie III undersökte vi huruvida för tidigt födda och fullgångna barn kunde bearbeta luktintryck, som även var irriterande, i olika delar av hjärnbarken. Vi undersökte om lukterna kunde leda till smärta och om administrering av en sockerlösning i munnen innan luktexponeringen kunde påverka smärtan. Vi exponerade spädbarn för lukter från sjukhusmiljön (handsprit och tejpborttagningsmedel), och registrerade aktivitet i hjärnbarken med fNIRS och smärtbeteenden. Vi upprepade exponeringen och mätningarna efter att barnen fått en sockerlösning i munnen. Nyfödda barn bearbetade både luktintryck och de irriterande delarna i de testade lukterna, både i luktområden och smärtområden i hjärnbarken från den 31: a beräknade graviditetsveckan och uppvisade också smärtbeteenden. Om de fick sockerlösning i munnen innan luktexponeringen minskade smärtsvaret i hjärnan och smärtbeteendena.

I studie IV studerade vi hur lukter från mammans bröst bearbetades i hjärnbarken, hos för tidigt födda och fullgångna barn, med fNIRS. Tre grupper av spädbarn inkluderades, mycket för tidigt födda (födda mellan v28-32), lätt för tidigt födda (födda mellan v33-36), och fullgångna. Barnen fick lukta på en snuttefilt som deras mamma burit vid bröstet under natten

innan testet och på en ren snuttefilt. Hos barnen födda efter fullgången graviditet fann vi att de aktiverade sina luktområden i hjärnbarken under tiden de luktade på sin mammas doft. Lätt för tidigt födda barn hade en ensidig aktivitet i luktområden när de luktade på mammas doft. Hos de barnen som var födda mycket för tidigt såg vi bara aktivitet i luktområden hos pojkarna men inte hos flickorna.

Sammanfattningsvis fann vi att extremt för tidigt födda barn inte hade samma aktivitet i hjärnan när de tittade på ett känt ansikte som barn födda efter fullgången graviditet. Denna mätmetod kan utvecklas vidare för att i ett tidigt skede kunna hitta barn med risk att utveckla ansiktsblindhet och då kunna sätta in träning.

Nyfödda barn kan också bearbeta starka sjukhuslukter och lukter från sina mammor i hjärnbarken. Detta är ett tecken på att de är medvetna om lukterna och lukterna kan påverka hjärnans utveckling i ett tidigt stadie och starka lukter ger upphov till smärta. Med ökad medvetenhet hos sjukhuspersonal och föräldrar kan potentiellt smärtsamma stimuli minskas kring de nyfödda barnen och man kan uppmuntra till att de familjära lukterna runt barnen kan ökas.

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